# Neurology

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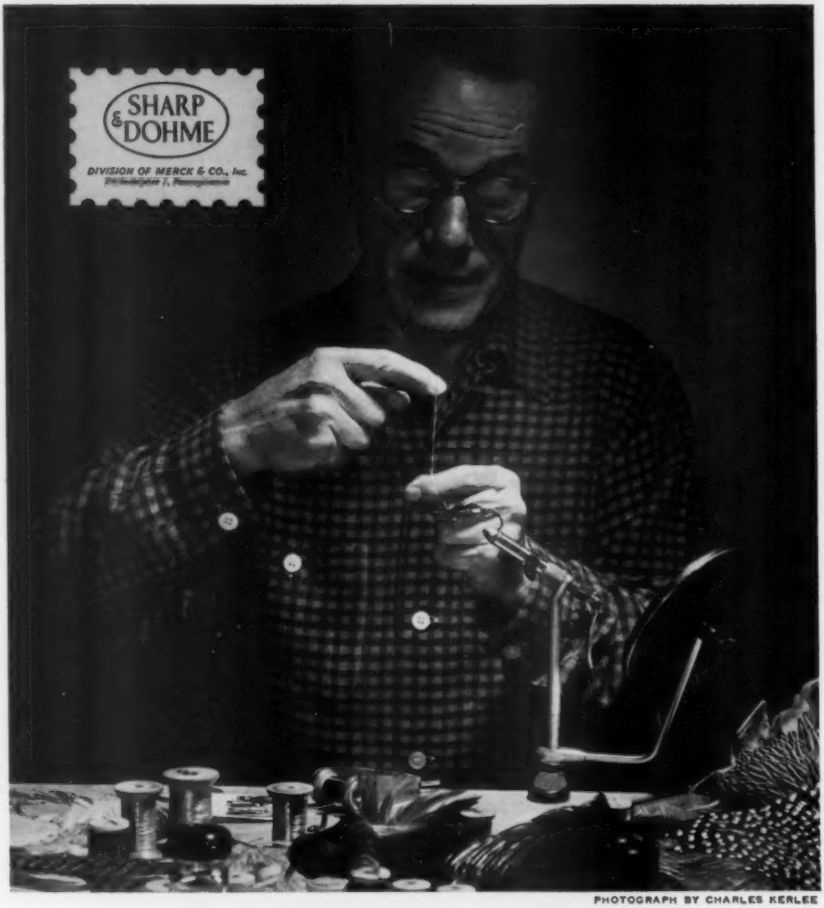


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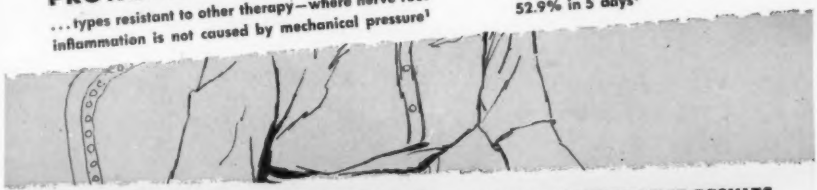

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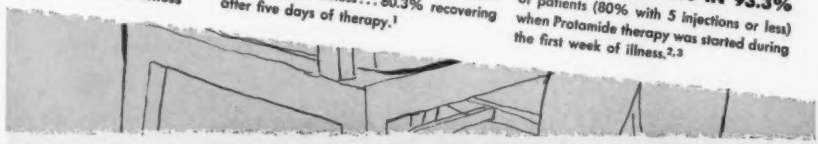

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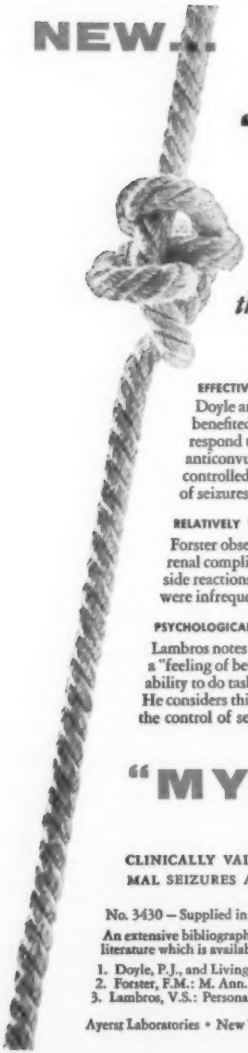

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1. Doyle, P.J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
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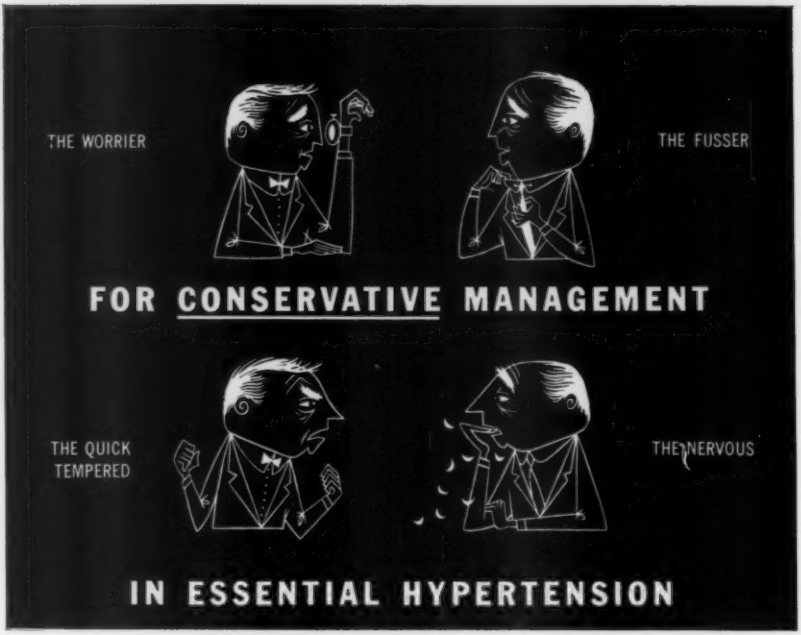


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# Neurology

## Puerperal Hemiplegia

*Harold Stevens, Ph.D., M.D.*

SUDDEN ONSET of headache, convulsions, hemiplegia, and coma occurring in a young, healthy woman several hours to several weeks after delivery is a terrifying and perplexing experience, especially if the obstetrician or neurologist is unfamiliar with this allegedly rare syndrome. Several excellent case reports on this phenomenon are recorded, particularly in the British[1–13] and French[14–16] literature, but the syndrome is rarely referred to either in texts or in the literature in general. The problem is not new. Hippocrates spoke of newly delivered women with some part of their body rendered powerless. Some authors consider it "rare and fatal," and according to Hyland[12] it is only in recent years that the condition has been diagnosed during life and that cases with recovery have been reported.

Eight cases are reported here, all in previously healthy individuals with no history, signs, or symptoms of toxemia, hypertension, or sepsis, ranging in age from 22 to 39. All recovered.

The semeiology of this condition consists of headache which is usually severe, appears early, and is often persistent; generalized or focal seizures, singly or repeated, are usually followed by focal paralysis, sometimes with aphasia; coma of varying duration is frequent. Papilledema may be present and the spinal fluid pressure is often elevated. A small or moderate number of red blood cells may be found in the spinal fluid. The following case typifies this syndrome:

*Case 1.*—A 25 year old primagravida was admitted to George Washington University Hospital on January 25, 1953 in labor. Her gestation was normal in every respect and she

From the department of neurology, Georgetown University Medical School, Washington, D. C.

Read at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 30, 1954.

never developed any hypertension, albuminuria, or edema. About one month prior to delivery she had had a cold, and a few weeks before delivery she had had treatment for an abscessed tooth. She was Rh positive.

After a low forceps delivery with spinal anesthesia, the patient complained of severe headache and numbness of the left side of her face. The blood pressure was noted to be 200/120. This was reduced with ether anesthesia and 2 gm. of intramuscular magnesium sulfate, but 30 minutes after this treatment it rose to 200/120 again. She was given 100 gm. of glucose in a 20 per cent solution intravenously. The pressure dropped gradually and over a period of several hours reached 115/75. At 1:30 p.m. on January 26 she developed a generalized grand mal seizure.

The neurologic examination done seven hours later showed no nuchal rigidity, no bruit, and the carotid arteries were pulsating. Coordination was unimpaired. There was weakness of the right arm and hand and slight weakness of the right leg. The cranial nerves were intact aside from nystagmus, dilated pupils, and slight facial asymmetry. Sensation was normal. The deep tendon reflexes were increased, more so on the right. There was bilateral patellar clonus and a positive strong right Babinski sign, none on the left. The Hoffman sign was strong on the right. There was no aphasia.

The neurologic diagnosis at that time was cerebral venous thrombosis. Spinal fluid examination was requested, as well as skull roentgenograms, nonprotein nitrogen and blood urea determinations, and examination of the urine for fat. Anticonvulsants were prescribed. The spinal fluid was colorless, clear, and showed a pressure of 230 mm. of water. The protein content was 79 mg. per cent; cell count two; colloidal gold, flat; nonprotein nitrogen and urine were normal. For a day following the convulsions, the patient remained somewhat confused but the neurologic examinations were completely negative. However, at 10:00 a.m. on January 29 the patient complained of a sudden onset of severe headache. One-half hour before, the blood pressure was 130/88, but was noted at this time to be 170/105. While being examined, the patient developed a left-sided clonic convulsion beginning in the arm and spreading to involve the entire left side. She received 250 mg. of phenobarbital and 30 gm. of magnesium sulfate intravenously, with cessation of the convulsion but the headache persisted. A bilateral ankle and knee clonus was present after the convulsion. Intermittent severe headache continued, and at 11:00 p.m. on February 2 the patient awakened with a very severe, pounding headache over the left occipital region. The blood pressure at that time was 160/95, and about three hours later she had a grand mal seizure that was generalized. According to the patient, she felt numbness in the left hand which spread upward to involve the entire limb, at which time she noticed the left arm was shaking and she then lost consciousness. A Babinski sign was found on the right side at that time. The spinal fluid examination was repeated after this seizure and initial pressure of 190 mm. was found. This procedure was done at 4:00 p.m. and immediately afterward the patient had another seizure. The spinal fluid showed protein of 54 mg. per cent, sugar 55 mg. per cent, and cell count two white blood cells. At 12 noon the next day the patient had a feeling of apprehension, and described numbness and tingling and uncontrollable twisting up the left arm, to the neck, face, and head, from there to the left hip, left flank, and left knee. The march took place in about four to five minutes but was not associated with any convulsions. She continued to have headache at that time and blood pressure was 150/95. These episodes of left-sided sensory-motor attacks continued over the next several days and repeat neurologic examination showed intermittent positive right Babinski sign.

Because of the history of treatment of a dental abscess, it was considered desirable to rule out brain abscess, and a pneumoencephalogram was done, which was normal. The patient was kept on anticonvulsant drugs but on February 9 she was still having periodic sensory-motor attacks. Blood pressure at that time was 150/110. Severe intermittent headaches continued, often interfering with sleep and requiring opiates.

Various blood and urine studies during hospitalization were completely negative.

Roentgenograms of the skull were negative. Repeat spinal fluid examination on February 11 showed a cell count of six red blood cells, 52 mg. of protein, and 750 mg. of chlorides. The colloidal gold was flat. Electroencephalograms on January 18 and on February 2 were normal.

Headaches and other symptoms gradually subsided, and the patient was discharged from the hospital on February 17, 1953.

This case illustrates most of the previously reported phenomena that constitute the syndrome of postpartum hemiplegia, including severe headache, repeated focal seizures, and transient signs of bilateral cerebral involvement. Spinal fluid pressure was elevated and minimal pleocytosis was present. The course showed fairly prompt resolution of all signs and symptoms except persistent headache, which disappeared over several weeks. Neurologic follow-up examination has demonstrated no residual defect and the electroencephalogram is normal.

The widely fluctuating hypertension (figure 1) observed in this patient has not been mentioned in prior reports, and will be commented upon further. Headache and convulsions often coincided with the high blood pressure. It is possible that the peak pressures might have been missed if blood pressure readings had not been taken at such short intervals.

As noted, the neurologic diagnosis was cerebral venous thrombosis. This is generally conceded to be the etiology in this syndrome. The subsequent progression of signs of bilateral cerebral involvement with increased cerebral spinal fluid pressure justified the further deduction that propagation of the venous clot extended from a large cortical vein to the sagittal sinus. Although confirmation of this venous thrombosis by direct visualization was not obtained, the symptomatology and course in this patient conformed so precisely with the more or less stereotyped clinical pattern reported by others that this

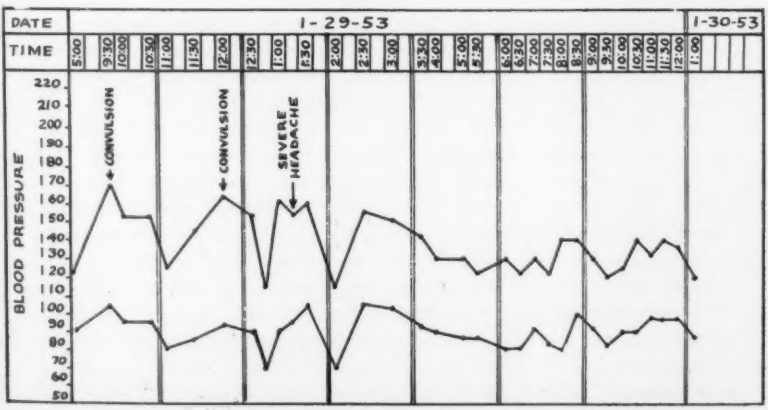


FIG. 1. The peaks of the high and fluctuating blood pressure corresponded at times with exacerbations of neurologic signs and symptoms in case 1.

inferential diagnosis was safely warranted. The etiologic role of cerebral venous thrombosis in puerperal hemiplegia has been demonstrated by craniotomy[3,4,17] and at autopsy.[5,7,9,12,14,17–20] A case similar to the one described above was reported by Symonds,[3] occurring 14 days postpartum. Two months later, because of persistent headache, a craniotomy was performed, revealing an old venous thrombosis with local cortical softening. Martin and Sheehan[4] reported four cases, three with autopsy. One showed thrombosed cortical veins in the right prefrontal area associated with small areas of hemorrhage and an area of early cortical softening. Another had thrombosed veins in the precentral gyrus with "rat-tail thrombus" in the superior sagittal sinus. Their third case died three years after the acute onset and showed only three depressed areas of cortical scarring.

Ramsey Hunt[21] recorded a case of a 21 year old primipara who, on the twentieth day postpartum, suffered sudden onset of headache, vomiting, convulsion, right-sided paralysis, and aphasia. Ten days later the autopsy showed extensive thrombosis of dural sinuses, including the superior longitudinal sinus, the lateral and petrosal sinus. There was also thrombosis of cortical veins with extensive hemorrhage and softening, especially over the frontoparietal region. Collier,[22] who was probably the first to recognize this entity in 1891, reported a patient who had focal convulsions 16 days postpartum, and at autopsy eight days later soft clots were found in the superior longitudinal sinus, the torcula Herophili, the right superior petrosal vein, and in the right hemisphere.

Further accounts are found in the older neurologic literature including that of Gowers[23] who listed the "puerperal state" among the possible causes of primary venous thrombosis.

The specific cause for this nonseptic primary cerebral venous thrombosis in the pregnant, parturient, or postpartum patient remains unknown. One theory holds that the usual physiologic changes in blood chemistry during pregnancy are responsible for the intravascular clotting. This position was taken by Meniere[24] in 1828 in his treatise, "Observation and Reflection on Cerebral Hemorrhage Considered During Pregnancy, Both During and After Delivery": "The blood which distends the whole circulatory apparatus is charged with fibrin and with viscous material; it greatly stimulates the organs which it supplies and gives their physiology an unaccustomed vigor. This state of the blood, characteristic of pregnancy, is without doubt necessary to furnish the fetus with nutrient material, but as it is not always maintained within reasonable limits, it becomes the cause of a host of accidents."

Sinclair[1] also suspected that vascular thrombosis was secondary to alteration in blood coagulability. Von Hösslein[18] offered the same explanation and added that sudden emotion seemed to be an associated element in several of his cases.

It is generally agreed that in the last trimester clotting tendency is normally increased, the fibrinogen level being 40 per cent higher at term than in early pregnancy.[25] King[26] in his excellent comprehensive review of neuro-

logic complications of pregnancy referred to this possible mechanism, and Alpers and Palmer[27] in a similar earlier review of general neurologic complications of pregnancy mentioned slowing of the blood and also suggested that thrombophlebitis elsewhere in the body may play a causative role. Bacteremia, even though transient, may injure the endothelium and further militate towards thrombosis. Poupon in 1885 in his account of "puerperal aphasia" implicated "les petits microbes."

Embolism due to fat, air, amniotic fluid, or placental fragments has been described,[1,26,28] but there is no clinical or pathologic evidence that would justify attributing cerebral venous thrombosis to this etiology.

Pre-existing thrombophlebitis elsewhere in the body has been given considerable emphasis by Martin and Sheehan,[4] who invoked the explanation provided by Batson to account for propagation of particulate matter from the pelvic veins by way of the vertebral veins to the cerebral venous circulation. Batson's experiments[29] further showed that compression of the abdominal wall of the experimental animal propelled radiopaque fluid into the vertebral system above the zone of compression, demonstrating that this route was open for venous drainage. Analogously, this type of data permitted the conclusion that coughing or straining could force blood in the abdominal veins into the vertebral system. Similarly, a tight binder or straining, for example in defecation, in the puerperal patient could dislodge and force a fragment of clot into the vertebral veins. Martin postulates phlebitis elsewhere in the body as a necessary precursor in the preponderance of these cases, and this view is shared by others.[1,19]

Case 2 seems to suggest the possibility that the repetitive alterations in intraabdominal pressure, secondary to passive compression of the thoracic cavity while administering artificial respiration, might have impelled preformed clots into the vertebral veins.

*Case* 2.—The patient was a 31 year old white woman who delivered a healthy boy weighing 6 lb. 5 oz. on August 18, 1953. The pregnancy was completely uneventful except for apnea requiring vigorous artificial respiration. Delivery was by low forceps, using ethylene and oxygen anesthesia. Several hours later the patient lapsed into coma. Neurologic examination showed an extremely restless, semiconscious woman. The pupils were equal and dilated, the fundi negative. There was normal reaction to light and also consensually. All limbs could be moved. Biceps, triceps, and other reflexes were equal and normal, but there was a bilateral Babinski. The blood pressure at that time was 110/70. The spinal fluid examination was completely negative in every respect. The patient made a prompt and complete recovery within 24 hours. The right side of the thorax was discolored and roentgen examination of the right side of the bony thorax showed a nondisplaced fracture of the sternal end of the tenth rib. Transient cystopyelitis was noted before discharge from the hospital on August 30, 1953.

As in this last instance in which transient cystopyelitis was noted, mild or occult local infections were shown or suspected in four other cases, further suggesting a possible source of embolism or origin of transient bacteremia. With the effort of labor local clots or bacteria might dislodge and provide the nidus for an extending venous thrombosis in the cortical veins. Many authors have commented on the unique anatomy of these cortical veins and venous

sinuses that make them susceptible sites of predilection for thrombosis. Merwarth[30] summarized the anatomicophysiologic characteristics peculiar to the cerebral veins that militate toward thrombosis:

1. The complete absence of valves in the Rolandic veins.
2. The low pressure of the contained blood.
3. The effect of coughing or sneezing on the venous flow.
4. The acute, forwardly directed angle at which the group of veins in the parietal occipital area enter the sagittal sinus.
5. The tendency for the direction of flow in those posteriorly placed cerebral veins to be opposed to the direction of the current in the sagittal sinus.

Once initiated, all five factors may act in concert to increase the extent of an obstructive process.

Since the cerebral veins open into the longitudinal sinus through narrowed ostia, it is necessary to assume that longitudinal sinus thrombosis occurring secondary to cerebral vein thrombosis represents an extension of the primary clot which has first occluded the cerebral vein and then extended itself through this narrow entrance to the larger sinus stream. Martin[5] has emphasized this point and also remarked on the slower flow of blood and the irregularity of the walls and trabeculations of the sinus, all militating toward sedimenting of any clot that enters this sluggish stream. Martin also insisted that 1) in the absence of severe heart disease and hypertension, venous thrombosis is the most probable cause of hemiplegia in the puerperium; and 2) many, if not all, these cases have venous thrombosis elsewhere in the body.

Stuart[31] stated that thrombosis of a superficial cerebral vein may occur as an isolated phenomenon, but is usually associated with superior longitudinal sinus thrombosis.

The signs and symptoms that constitute the usual clinical constellation of puerperal hemiplegia have been enumerated, and case 1 illustrates the classical pattern. Other phenomena may also occur with varying frequency, particularly severe visual disturbances and psychic alterations. Cases 3, 4, and 5 demonstrate both of these complications added to the typical syndrome.

*Case 3.*—A 39 year old white woman was admitted to George Washington University Hospital on July 17, 1953 in labor which began at 3:15 a.m., at which time the blood pressure was 120/80. Nine hours later, a healthy 8 lb. 1 oz. boy was born after a normal course of labor, with no associated complications or difficulty during delivery. In the immediate postpartum period, the blood pressure was taken about every half hour and showed the following: 136/80, 136/82, 130/80, 128/78. Nembutal in two doses of 150 mg. and 250 mg. was given two hours before delivery, and ether with oxygen was the anesthetic employed. About 25 cc. of blood was lost during the second stage of labor and about 100 cc. during the third stage. The duration of anesthesia was about 20 minutes.

The patient had delivered four other children, of whom one was mentally deficient and one died 45 minutes after birth with multiple congenital anomalies. It had been 15 years since her last previous pregnancy. The patient had been in perfect health during pregnancy and had never suffered headache, visual disturbance, or edema. There was no albuminuria or hypertension during this or any other pregnancy. One week postpartum, the patient was discharged in excellent health. Five days later throbbing headache developed. It was constant and severe, not relieved by any medication, and disturbed her sleep. The next morning she had an episode of aphasia associated with blurring of vision, particularly of the right visual field. Her physician found right facial weakness and a right

Babinski sign. There were no chills, fever, dysuria, frequency, or urgency. There was no history of any infection. She gave a lucid history on readmission to the hospital, then suddenly became aphasic and began to have a convulsion, with turning of the head to the right and jerking of the left upper extremity. The blood pressure at that time showed 190/80 in the right arm and 190/85 in the left arm. After the convulsion, which lasted one to two minutes, the fingers of the right hand remained clenched. Funduscopic examination was normal. The temperature was 98.6° F. rectally. After the convulsions she appeared lucid, although aphasic.

The neurologic examination after the seizure revealed no evidence of any focal disease of the central nervous system aside from the previously noted aphasia.

It was the opinion of one physician that this "represented a postpartum eclamptic episode." Other suggestions were essential hypertension and pheochromocytoma. The urea nitrogen was 10 mg. and carbon dioxide was 59 on July 30. Urine was negative. Spinal fluid examination the next day showed the initial pressure fluctuating between 130 and 140 mm.; 5 cc. of clear fluid was removed which showed two red blood cells, no white cells, 71 mg. per cent of protein. Colloidal gold was flat. Blood count was normal. The electroencephalogram on July 31 was abnormal, with foci in the right parietal and left temporal leads. On August 2 the blood pressure was 180/90 and this remained elevated and variable as noted in figure 2. Later the same day the patient was found lying on her side in bed, her face flushed, with saliva running down on the left side of her face. She was confused and restless. The pupils were enlarged. The bed was soaked with urine. She misidentified people about her and was disoriented. One hour later she was alert and responsive. Intermittent headaches required opiates for relief throughout her hospital stay. She was discharged in a normotensive condition on August 6, 1953 with no neurologic defects.

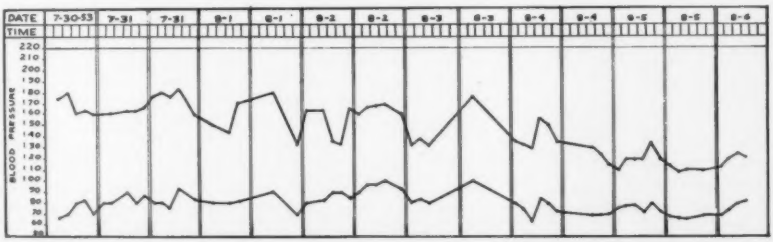


FIG. 2. Fluctuating hypertension in case 3 stabilized at normotensive levels in about one week.

*Case 4.*—A 29 year old woman with two children was admitted to George Washington University Hospital on June 13, 1949 because of severe headache which began 17 days after delivery of her last child. Pregnancy was uneventful, but the patient developed pyelitis about nine days after delivery which responded to three injections of penicillin. The headache developed suddenly at noon on the day of admission and did not respond to aspirin. It was most severe over the top of the head, progressive, and became associated with general malaise and intermittent vomiting.

On admission the patient appeared pale and lethargic. The blood pressure was 182/95, and the pulse was between 48 and 55. The eye grounds were normal and the rest of the examination was negative. There was no nuchal rigidity. The day following admission the headache had subsided but suddenly recurred, associated with loss of vision, weakness, and nausea. The blood pressure at that time was 200/100, and a left homonymous hemianopsia was present. The eye grounds were normal and there were no cranial nerve de-

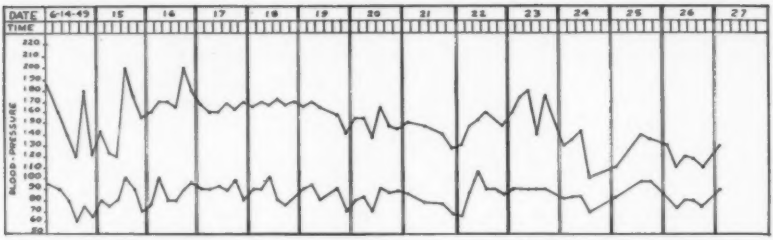


FIG. 3. Hypertension associated with neurologic involvement including left homonymous hemianopsia occurring 17 days postpartum, case 4. Patient remains normotensive.

fects. The reflexes were hyperactive, a positive Babinski and unsustained ankle and knee clonus were present on the left. There was slight weakness of the left lower extremity but no sensory defects. Spinal puncture was done at that time and showed an initial pressure of 210 mm., "many" red blood cells, and 60 mg. per cent of protein, 80 mg. per cent of sugar, 720 mg. of chlorides, and a first zone gold curve. No white blood cells were seen; blood urea nitrogen, carbon dioxide, and other blood studies were normal. The course was marked by frequent exacerbations of severe headache which required Demerol for relief. Nausea and vomiting persisted and the hypertension fluctuated, remaining at high levels for ten days (figure 3). On June 23 the patient was up and about, complaining of lack of coordination, poor vision, and difficulty with fine movements. A repeat spinal puncture was unsuccessful. The left hemiparesis persisted and the left hemianopsia gradually improved. The left Babinski and increased deep tendon reflexes on the left persisted. She continued to show psychomotor retardation, with obtunded intellectual processes. She was discharged on June 27, 1949, alert but with a left lower quadrant field defect.

*Case 5.*—A 32 year old woman was well during her pregnancy and delivered a normal child uneventfully at 9 a.m. on October 5, 1953. She complained of blurring of vision after the anesthesia wore off, and in a matter of a few hours she developed total blindness. Her blood pressure was 175/125 and continued to fluctuate at a high level (figure 4). Four hours after delivery, she was nauseous and became confused. There was weakness of the left arm and twitching of both hands. She became incoherent, excited, delusional, and demonstrated visual and auditory hallucinations. She thought she was in a silver bed, heard her mother in the hallway crying, and believed that she was being given poison and would soon die. She noticed little grey boxes moving up and down in front of her and saw ugly green masses of metal on the shoulders of the nurse. These phenomena continued for the next several days.

At 1:55 p.m. on October 6 the patient was given 6 minims of Veratrone and 45 minutes later she was given 4 more minims. The blood pressure fell and in a period of two hours was 110/60. However, the patient lapsed into coma and then gradually regained consciousness, at which time she complained of headache. She continued in and out of coma and blindness persisted. Three days later vision began to return but she remained apprehensive, at times disoriented, restless, and delusional. At times objects appeared very small to her and objects on the right side of her appeared to be on the left. The repeat neurologic examination showed only slightly increased deep tendon reflexes. The fundi showed no hemorrhages and no retinal detachment. X-ray of the skull was normal, and the spinal fluid was clear with 10 mg. of protein and 67 mg. per cent of sugar. Nonprotein nitrogen remained within normal limits and the urine was negative. No fat was found in the urine.

The patient had a mild transient pyelitis which responded to antibiotics. Her improvement was rapid after the first five days and she was discharged without neurologic or psychologic defect on the twelfth day after delivery in a normotensive condition. Follow-up

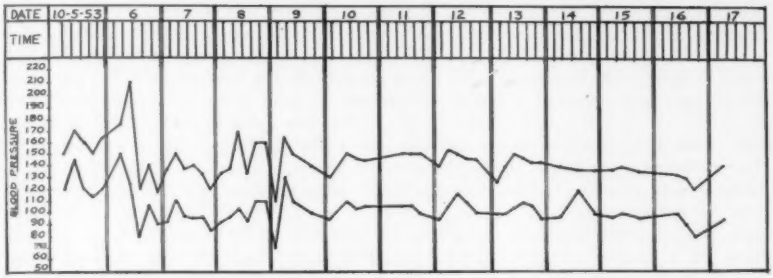


FIG. 4. Blood pressure readings recorded every four hours in case 5. The hypertension, associated with blindness and transient psychosis, gradually resolved.

neurologic examination and electroencephalogram have been negative. The patient was placed on anticonvulsant drugs and remains on them to date.

The visual symptoms that may appear with this syndrome usually represent sudden loss or impairment of visual acuity. This may manifest itself as a hemianopsia, typically contralateral to the cerebral lesion and reflecting interruption of the geniculocalcarine tract; or the visual loss may be complete and generalized in one eye or both due to optic nerve damage. Papilledema frequently accompanies the other phenomena and may cause or contribute to visual impairment. Carpenter and co-workers,[32] in their report on the development of blindness as a complication of pregnancy, recognized intracranial venous thrombosis as a potential cause of blindness. Martin[5] described a case of decreased visual acuity, probably due to venous congestion of the optic nerve head. The amaurosis cleared but was followed by word blindness.

Case 5 was at first considered to have a postpartum psychosis and transferral to a psychiatric hospital was contemplated. This was indeed a postpartum psychosis but certainly not in the conventional sense. Clinically, it was a typical organic psychiatric syndrome that simulated delirium tremens or any acute toxic psychosis. As noted, there were vivid auditory and visual hallucinations which were extremely distressing to the patient and augmented her anxiety. Characteristically, she could at times recognize the endogenous nature of these experiences, while at other times, particularly at night, she accepted them as real. Misinterpretations, paranoid elaborations, and disorientation were also manifest.

When confusion and disorientation is coupled with aphasia, the picture may be misconstrued as a psychosis. Closer observation in most instances results in segregation of these factors; also aphasia is always suspected with co-existent right hemianopsia. A variation on this pattern was provided by the following patient who actually had no true psychiatric syndrome but demonstrated rather a typical and transient anosognosia and autotopognosia. These latter lasted four days and then resolved quickly.

*Case 6.*—A 29 year old woman had had two spontaneous abortions and one normal healthy child. The pregnancy was normal in every respect with no evidence of hyperten-

sion or toxemia. At 2:00 p.m. on May 19, 1952, the patient was delivered by a controlled, spontaneous delivery in bed in the delivery room. She fell asleep after the delivery, but five and a half hours later it was difficult to rouse her, and on waking she was drowsy and noted to have a left hemiplegia. The blood pressure at that time was 104/70. The neurologic examination showed a dextral woman with no prior history of neurologic disease. Head showed no bruit and no nuchal rigidity. There was a left hemiplegia that was complete with slight spasticity in the left arm and a flaccid left leg. There was left autotopognosia and anosognosia. The disks were flat and vessels normal. No hemorrhages or exudates were present. The pupils were dilated and reacted to light and in accommodation. Extraocular movements were normal. There was no ptosis. There was a central left facial weakness and dysarthria. The deep tendon reflexes were increased on the left and there was a positive Babinski and all confirmatory tests on the left side. A diagnosis of cerebral venous thrombosis was made; aneurysm was still to be ruled out.

The spinal fluid examination showed a slightly yellowish fluid with a cell count of 10,080 red blood cells. The protein was 196 mg. Spinal fluid pressure was 80 mg. The fluid was pink in all three tubes.

The patient showed a marked and rapid return of power in the arms and legs, but nuchal rigidity persisted. This latter gradually diminished.

Repeat neurologic examination showed an alert, well-oriented woman with a left hemiparesis. There was slight nuchal rigidity and a slight positive Kernig sign. There was hypalgesia of the left arm and leg.

The neurologic examination on May 26 showed a marked diminution in nuchal rigidity. Blood studies were done to exclude hemorrhagic diathesis. On May 31 there was slight central facial weakness on the left and the left leg "felt different." On June 3 dysesthesias and numbness of the left leg were still present. The electroencephalogram on June 4 was highly and diffusely abnormal, with almost constant irregular slow activity in the right anterior areas and paroxysmal bursts of regular slow activity in the left anterior areas.

The patient declined arteriography. She continued to suffer severe headaches and it was necessary for her to take codeine, 65 mg. three times daily. She was discharged on June 9 with minimal weakness of the left side and marked improvement in her headaches. Follow-up electroencephalographic studies have been normal. The headaches disappeared within three months, but there is still slight left facial weakness and decreased acuity in the left eye.

As noted in this case and in case 5, onset was within a few hours after delivery. Other reports indicate that onset may occur with delivery or up to seven months afterward. Most range between one day and two weeks, however.

In case 7 the patient reported in retrospect that she suddenly felt her left side go numb just before delivery of the infant's head. She tried to inform the attending physician, but at this moment the anesthetist clamped on the mask and her complaints were unheard.

*Case* 7.—A 22 year old primigravida had an uneventful pregnancy with no evidence of hypertension, edema, albuminuria, or infection. On June 28, 1943 a normal child was delivered under ether anesthesia. On regaining consciousness, the patient was noted to have a complete left hemiplegia. This improved rapidly over the next several days. Repeated neurologic examinations were done and over the ensuing year most of the residuals resolved. The last neurologic examination was four years after her delivery, at which time a Babinski and Chaddock's sign persisted and there was a positive Hoffman and positive thumb sign on the left, but no other defects.

The time of onset in relation to termination of pregnancy was recorded in these eight cases and compared with postpartum nontoxemic cases found

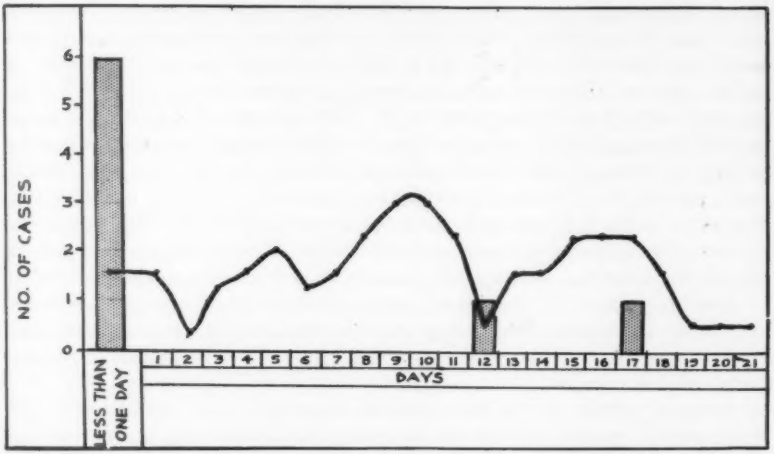


FIG. 5. The days after delivery of onset of puerperal hemiplegia of 39 cases found in the literature are represented by the smoothed frequency curve. The stippled blocks represent day of onset of the author's eight cases.

in the literature (figure 5). In contrast to the previously reported cases, the apparent earlier onset recorded in most of these eight cases might reflect skepticism by the individual obstetricians of the diagnosis "postpartum eclampsia" and thus neurologic opinion was sought. Case 7 also illustrates the favorable prognosis characteristic of this series.

The nonfatal outcome in all eight instances seems to warrant more optimism than has been expressed previously and is in particular contrast to the ominous prognosis given in the older literature on this subject. Regarding the question whether subsequent pregnancies are safe, further statistical appraisal is required. Data on larger number of patients followed over a longer period of time would be enlightening. Case 8 has had the longest period of observation, having delivered a healthy child in 1940 with subsequent hemiplegia that receded over a period of several weeks. Because of this experience she avoided further pregnancies.

Morbidity is low, but lowered threshold to convulsions is a possible sequela.[11,20,26,31,33]

Diagnosis is easily established and would probably be recorded more often except for general unfamiliarity with this syndrome. Frequently neurologic consultation is not sought because the label "postpartum eclampsia" is affixed and seems to satisfy the circumstances and the attending physician. However, this etiology is not defensible in the face of complete absence of signs of previous toxemia, especially in cases that occur several days after delivery. Various diagnoses were made in the eight cases reported here, including postpartum eclampsia, cerebral (arterial) thrombosis, brain tumor, abscess, hys-

terical hemiplegia, postpartum psychosis, and cerebral aneurysm. Many of these must be considered in the differential diagnosis, particularly intracranial aneurysm, the occurrence of which with pregnancy has been a subject of recent interest. However, aneurysm occurs no more often in pregnancy than in other individuals of the same age.[34] The question of cerebral aneurysm would seem particularly cogent in case 6, where the onset seemed temporally related to labor and where subarachnoid bleeding was demonstrated. However, one would expect more prolonged and devastating effects, including cranial nerve signs, if a ruptured aneurysm was responsible for the hemiplegia, hemianesthesia, and disturbance in body image. Conversely, cerebral venous thrombosis is known to frequently cause subarachnoid hemorrhage.[8,12,30,35,36]

Cerebral arterial thrombosis is quite unlikely to occur in a young healthy individual, and again would be expected to produce shock-like state and cause more lasting effects. None of these eight patients showed evidence of disseminated vascular disease.

Cerebral anoxia due to the anesthetic agent was also considered in the differential diagnoses, but this could not explain the late development of neurologic symptoms, and again the clinical (and pathologic) pattern is quite different.[26,37,38]

Examination of the spinal fluid is helpful. Elevated pressure is a frequent but not a constant finding. When present, it may be due to isolated cerebral vein thrombosis or reflect superior sagittal sinus involvement, simulating the syndrome caused by obstruction or compression of the sinus from other causes, for example trauma or tumor.[35,39] The sagittal sinus in cross section is triangular and divided by a horizontal septum, the upper half of which contains spinal fluid destined to be absorbed by the Pacchionian bodies with which the upper half of the sinus communicates.[40] If the flow or absorption of the cerebrospinal fluid is embarrassed by compression or clot in this upper compartment, intracranial pressure will rise and headache with papilledema will result.[5] Some authorities[4,30,31,35] have found a correlation between clinical manifestations and the site of venous thrombosis, for example weakness of both lower limbs is commonly found with sagittal sinus thrombosis; involvement of the face, hands, fingers, and arms, often with aphasia, implies thrombosis of a cerebral vein over the lateral convexity; isolated paralysis of the upper extremity indicates thrombosis of the vein in the Rolandic gyrus; and with extension of the thrombus upward, it is to be expected that the contralateral leg would be affected.

Depending on the anastomotic pattern, venous drainage may readjust its flow and there is return of function in the involved limbs. Another variable that may influence the clinical picture and outcome of sinus thrombosis is the rapidity with which occlusion occurs. Gradual occlusion may occur without fatality, even without producing focal signs.[30,35,41]

Headache was a conspicuous and early symptom, often persisting for many weeks. In the first ten days following the acute onset it was often associated with elevated blood pressure. As stated, this widely fluctuating hy-

pertension was present in four of these eight cases. Pheochromocytoma was excluded in two cases by chemical tests and by the subsequent course.

Convulsions may be generalized or focal and may be the first sign. They often follow a rise in blood pressure. The electroencephalogram may be abnormal. Follow-up tracings in three cases were normal, but all three patients remained on anticonvulsant drugs. According to Barnett[13] venous thrombosis should always be considered when convulsions occur in the postpartum period.

In this connection, two patients not included in this series had postpartum convulsions, but they were associated with only minimal neurologic signs. In one of these patients, convulsions occurred three weeks after delivery, followed by impaired memory and confusion that lasted one week. A second convulsion one week after that was again followed by confusion and memory defect that was more profound and then gradually receded. The second patient had a convulsion four days postpartum associated with vertigo, headache, and nuchal rigidity. Neither patient had had prior seizures. No positive inference can be drawn, but these two cases suggest that perhaps milder forms of venous thrombosis can occur with seizures as the only striking manifestation.

Fortunately, all of these cases survived and postmortem verification of the diagnosis is not available. In a sense, the diagnosis remains inferential but justified on the grounds already given. Angiography might have been of interest, but probably would be hazardous because of the already damaged and probably labile cerebral vessels. Sinus venography, as described by Ray,[41,42] would probably be enlightening in this syndrome.

Treatment is oriented toward 1) resolving and limiting the extension of the thrombus, 2) lowering the intracranial pressure, 3) lowering the blood pressure, and 4) preventing convulsions.

In recent years therapeutic agents have evolved that help to accomplish some of these objectives, in contrast to the less plausible but more vigorous measures that were available a hundred years ago when Churchill[43] in 1854 described his management of hemiplegia associated with pregnancy: "Leeches were immediately applied to the temples and the bowels were well freed as soon as possible, a large quantity of dark feces being expelled. When this was effected, she was rubbed with mercurial ointment and leeches were again applied to the temples and behind the ears followed by blisters to the nape of the neck and behind the ears. She was quickly brought under the influence of mercury and severe salivation ensued. The power over the limbs soon began to return and were it not for the severity of the action of the mercury on the mouth, she could have spoken."

The latter day therapists are relatively more conservative in their approach:

1) To achieve the primary objective of resolving and preventing propagation of the cerebral venous clot, anticoagulants have been employed with the same rationale for which they were originally introduced for intravascular clotting elsewhere in the body. One serious obstruction to their routine use

in puerperal hemiplegia, however, is the real danger of producing uterine or cerebral bleeding. For this reason anticoagulants have been interdicted by some.[11,13,33] In the eight cases reported here, all recovered without anticoagulant therapy, suggesting that the danger inherent in their use does not justify the risk.

2) The rise in intracranial pressure, secondary to the cerebral edema and congestion due to venous thrombosis, is combatted with the conventional measures employed in other situations where this complication arises, for example the use of intravenous hypertonic glucose. Recently, experience with concentrated serum albumin indicates that it can effect the desired dehydration also. But in the puerperal period, particularly immediately postpartum, the risk of intravascular clotting might be enhanced further if blood viscosity were increased.

Repeated lumbar puncture with withdrawal of spinal fluid has been recommended,[3,5,11] but this introduces the hazard of possible tamponade of the brainstem.

The efficacy of temporal decompression is undetermined, and there is no body of data at present that would warrant its routine use. Resection of a thrombosed Rolandic vein of unknown etiology was successful in one case reported by Guillaume.[44] The craniotomy itself or the ventricular drainage by relieving intracranial pressure may have been responsible for the beneficial effect of the surgery, rather than the venous resection.

3) The high and widely fluctuating blood pressure recorded in four of these cases suggests that this is another complication imposed by cerebral thrombosis and in itself might be inimical to the patient's already disordered economy. It might seem reasonable then to employ the recently developed hypotensive drugs. But, if the vascular hypertension is determined reflexly and designed to overcome the increased cerebrovascular resistance due to elevated intracranial pressure, removing this hypertension with drugs would nullify this protective reflex and cerebral blood flow would fall correspondingly. On this basis the propriety of using hypotensive drugs is open to serious question. Further, if hypotensive drugs are harmful in cerebral venous thrombosis, it becomes even more exigent to distinguish this condition from the hypertension found in toxemia of pregnancy in which these drugs are commonly employed.[45,46]

As stated, since vascular hypertension in cerebral venous thrombosis is the reflex response to rise in intracranial pressure designed to spare the vital medullary centers from ischemia, reducing this vascular head of pressure in the face of increased intracranial pressure would be expected to dangerously diminish cerebral blood flow. Recently Kety and co-workers[47,48] have experimentally confirmed and quantitated this Cushing phenomenon. They demonstrated in humans a high correlation between intracranial pressure and mean arterial pressure (r-0.86), and further showed that cerebral vascular resistance increased with rising intracranial pressure (r-0.83). In the absence of the compensatory rise in blood pressure, progressive decrease in cerebral blood

flow would result.

The use of Veratrone in case 1 was associated with a drop in blood pressure followed by coma in two instances. This suggests the operation of the above principle, but it certainly is not conclusive.

4) Convulsions, which may be the initial event that signals the venous thrombosis, may also appear during convalescence. Prompt use of analeptics in the acute crises is required. The exertion associated with the convulsion adds further stress on the entire organism and specifically raises intracranial pressure further. Sodium phenobarbital 0.12 gm. intramuscularly should be given at once and repeated as often as necessary to halt the seizures. Oral Dilantin and phenobarbital should be continued for an indefinite interval, depending on the clinical and electroencephalographic residuals.

SUMMARY

Eight cases of postpartum hemiplegia are reported with the implication that this condition is not rare but is often misdiagnosed as postpartum eclampsia, a diagnosis which is indefensible for the reasons cited. More frequent request for neurologic consultation would probably alter the statistics for this condition.

Diagnosis can be made easily. The semeiology consists of sudden onset of headache, convulsions, coma, and hemiplegia, appearing several hours to several weeks after delivery in a previously normal patient. Blindness and mental symptoms may coexist.

A previously undescribed further feature of this syndrome is fluctuating hypertension, the mechanism and management of which is discussed with particular reference to the use of hypotensive drugs. If this hypertension occurring with convulsions and other neurologic symptoms is misconstrued as eclampsia and hypotensive drugs are employed as is frequently done in eclampsia, serious embarrassment of cerebral blood flow would result. Thus the necessity for correct recognition of this syndrome is further emphasized.

The cause of puerperal hemiplegia is cerebral venous thrombosis. This has been documented by direct observation after craniotomy and at autopsy in cases previously described, particularly in the British literature.

The prognosis appears better than previously reported. All eight cases survived. Morbidity was low but susceptibility to seizures is probable.

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# Role of Hypothalamic Mechanisms in Thalamic Pain

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THE MECHANISM of the Dejerine-Roussy syndrome is obscure. The original view of Roussy[1] that the pain and hyperpathia are due to an irritation of the involved parts of the thalamus has already been contradicted. Head[2] has pointed out that most of these cases are due to vascular disturbances that produce the maximum symptoms immediately after the cerebrovascular accident, while the characteristic symptoms of the thalamic syndrome develop at a much later time, when the patient has recovered from the direct effect of the vascular lesion. But Head's assumption of a release of the lateral part of the thalamus from cortical inhibition could not be maintained. Experimentally cortical stimulation[3] as well as ablation[4] failed to show the existence of a cortical inhibition of thalamic discharges, and also the absence of thalamic pain in cases with large lesions of the internal capsule mitigates against Head's theory. Similarly the hypothesis of a release of the thalamus from a striopallidal inhibition[5] is not acceptable, since in most diseases of the striopallidum or of its efferent fibers pain is not present. Likewise in our material with pallidotomy and ansotomy, pain did not occur.

Many authors have been attracted by the theory that the phylogenetically young epicritic sensation inhibits the phylogenetically old protopathic sensation (for peripheral nerves: Rivers and Head,[6] for thalamic pain: Foerster[5]). However, in the majority of cases with degeneration of the posterior column pain does not appear. Instances of spontaneous pain without a lesion of the epicritic sensation have been observed as well as elimination of the epicritic system without hyperpathia.[7–11]

Of particular interest is Lhermitte's[12] view that the thalamus has a filter function, and that destruction of this filter results in the conduction of impulses to the cerebral cortex that normally are retained by the thalamus. The opposite view was expressed by Wallenberg,[13] who believed that pain im-

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pulses cannot pass the injured thalamus. Schuster[14] has already pointed out that there is no analogy in neurophysiology for a mechanism which causes the facilitation of the conduction of impulses through an injured area of gray matter. It should also be mentioned that the conduction of pain impulses to the cerebral cortex apparently is not the significant factor in the pathogenesis of the thalamic pain, since neither excision of the sensory cortical areas nor prefrontal lobotomy prevent or abolish this type of pain.[15] In view of these difficulties which the prevalent theories of thalamic pain have been unable to overcome, it seemed of interest to try an experimental approach to this problem based upon the following considerations.

A number of clinical observations seem to suggest that the hypothalamus may play a role in the genesis of the Dejerine-Roussy syndrome. Thalamic pain may be elicited or increased by psychic influences; the affective character of the thalamic hyperpathia and the overloading of the sensation with feeling tone often are very striking. Frequently the vegetative nature of thalamic pain has been noted, and it has even been compared with causalgia.[16] Lhermitte[12] and Schuster[14] emphasized the frequent association of the Dejerine syndrome with vasomotor and other vegetative disturbances.

From experiments of Karplus and Kreidl[17] in the cat and monkey we know that hypothalamic stimulation may induce pain suggestive reactions, and anatomic as well as physiologic studies have shown that sensory impulses are able to reach the hypothalamus. Johnston[18] and Wallenberg[19] were probably the first who pointed to the fact that afferent, particularly vegetative, impulses are able to enter the hypothalamus, and LeGros Clark[19] stressed the particular development of afferent pathways from the viscera to the hypothalamus in lower vertebrates. He pointed out that the hypothalamus is the recipient of impulses on the basis of which the organism may develop an awareness of its internal organic activities and through which sensory experiences are endowed with an affective tone. By recording the electrical discharges an influence of afferent impulses upon hypothalamic activity could be shown in mammals on stimulation of somatic [20,21] as well as of vegetative nerves.[22, 22a,b,c] Therefore it seemed of interest to study experimentally the effect of thalamic lesions upon the electrical activity of the hypothalamus and upon the evoked potentials lead off from this area on sensory stimulation.

In planning the experimental thalamic lesions it was essential to clarify which thalamic nuclei are regularly involved in the Dejerine-Roussy syndrome. There seems to be some agreement at least, in that the syndrome usually results from vascular disturbances in the area of branches of the posterior cerebral artery,[23] especially the arteria thalamogeniculata. In the older literature[24] one often finds the statement that, of the thalamic nuclei supplied by this artery, particularly the lateral or external nucleus is affected. However, one has to bear in mind that the older nomenclature included the ventral nuclei as part of the lateral nucleus. An analysis of previous case reports[25] clearly showed that a lesion of the dorsal part of the ventrolateral group of nuclei (of the lateral dorsal and posterior nuclei) is not essential for the development

of the thalamic syndrome, but that a lesion of the ventral posterior nuclei, that is, of the endings of the long ascending sensory pathways from spinal cord and medulla oblongata, induces this syndrome. This is in agreement with Roussy's original description and also with more recent observations.[26,27] It was therefore decided to produce the thalamic lesions in the area of the ventral posterolateral nuclei.

## METHOD AND MATERIAL

Two groups of experiments were performed, acute experiments in 16 cats and chronic experiments in ten cats.

In the acute experiments, the cats were prepared under Surital anesthesia; usually 0.6 cc./lb. of a 2 per cent solution of this drug was used. After cannulation of the trachea and the saphenous vein and exposure of the sciatic nerve, a plastic plate electrode carrier[28] was fastened over a trephine opening in the skull and guide holes were drilled through the plate at the chosen coordinates by a drill fixed to the stereotaxic apparatus. After allowing 30 to 45 minutes for recovery from anesthesia, curare (Intocostrin) was injected into the cannulated vein and artificial respiration was instituted. The recording electrodes (bipolar concentric needle electrodes) or multilead electrodes, similar to those described by Epstein,[29] were inserted into the hypothalami. For recording of potentials from the hypothalamus evoked by stimulation of sensory nerves (ulnar, superficial cutaneous antibrachii, sciatic), the optimal position of the recording electrode was at an average distance from the midline of 1.5 to 2.5 mm. and at a depth of 20 to 24 mm. below the cortex. The animals were studied either unrestrained or suspended in a hammock. Thalamic lesions were made with the stylet electrode described by Spiegel and Wycis,[30] through which was delivered a direct current of 10 ma. for 1 minute for each lesion. In some instances the experiments were performed in two stages. In these cases the electrode carrier was applied while the cat was under Nembutal anesthesia. The following morning the cannulations and exposure of nerves were carried out under ether anesthesia. Time was allowed for the cat to blow off the ether and curare was injected, at which time recording electrodes were inserted.

For the chronic experiments lasting as long as six months, the electrodes used were insulated silver wires, .0055 inch (.14 mm.) in diameter. The exposed end of each wire was folded several times, so that a band of 0.5 to 1 mm. width was formed (figure 1).

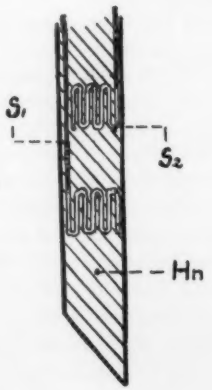



FIG. 1. Recording electrodes ($S_1$, $S_2$) fixed on insulated hypodermic needle (HN). $S_1$ indicates the insulated part of the one electrode and $S_2$ the blank part of the other electrode.

These silver wires are fixed by means of a viscoloid solution to a hypodermic needle (26 gauge, 1½ inches long). The folded ends are wound around the needle at a distance of 1 to 2 mm. from each other. Under Nembutal anesthesia the hypodermic needle with the electrodes is inserted into the brain through a drillhole in the calvarium, by means of the stereotaxic apparatus; the tip of the needle is pushed into the base of the skull so that fixation of the needle with its electrode wires is insured. The upper end of the needle is then cut and fixed in the drill hole with dental cement. The extracranial part of the silver wires, which is covered by thin polyethylene tubes (external diameter 1.2 mm.) is tunneled below the skin to the neck where the wires emerge. During their course, these wires with their polyethylene sheaths are knotted several times; (at a distance of about 2 cm. from the drill hole, in the occipital region and in the neck). These knots prevent undue movments of the wire and supply reserve wire should the free ends be torn off.

Recordings were carried out on unanesthetized animals suspended in a hammock. Sometimes bulbocapnine catalepsy or Nembutal anesthesia was used. For stimulation of various nerves, segments of surgical stainless steel needles protruding from a flat plexiglass holder proved useful. The holder could be fixed by adhesive tape to the extremity and exposure of the nerves was usually not necessary. A Grass stimulator, model 3C, was used. Usually square wave pulses of 1 to 10 msec. duration, 0.6 to 4.0 V. in intensity were applied. In all experiments recordings were made with a three channel EEG apparatus. The extent of the lesions and positions of the electrodes were studied macroscopically, and in important cases serial sections were stained with Weil's myelin stain.

## RESULTS

In acute experiments conducted one to three hours following the thalamic lesions, one observed changes in the spontaneous electric activity of the hypothalamus and/or of its reactivity to afferent impulses. In some cases the spontaneous discharges showed signs of depression or no definite changes, in the others signs of increased activity were noted (figure 2). In the latter group, there was an increase in the amplitude and/or the frequency of the spontaneous discharges. In some instances slow waves (for example, 3/sec.) recorded from the hypothalamus before the thalamic lesions disappeared following such lesions and were replaced by discharges of higher frequency and lower amplitude (desynchronization).

Regarding the effect of the thalamic lesions upon the evoked potentials recorded from the hypothalamus on homolateral or contralateral peripheral stimulation, it should be pointed out that even with the thalamus intact the amplitude of these evoked potentials often showed rhythmic fluctuations on repeated stimulation at one second intervals (figure 3). Sometimes spontaneous changes of their direction could be observed; for example, on bipolar recording from a dorsal and a ventral point of the hypothalamus one could first observe that the dorsal point was negative (or positive) in relation to the ventral one, while in the further course of the experiment the direction of the monophasic spike became reversed. Sometimes a biphasic spike appeared between these reversed spikes (figure 3).

Following a lesion of the ventral posterior thalamic nuclei, one could observe, either associated with the changes in spontaneous activity or independent of them, an increase of the amplitude of the evoked potentials (figure 4) or changes in their type (for example, wider base), or evoked poten-

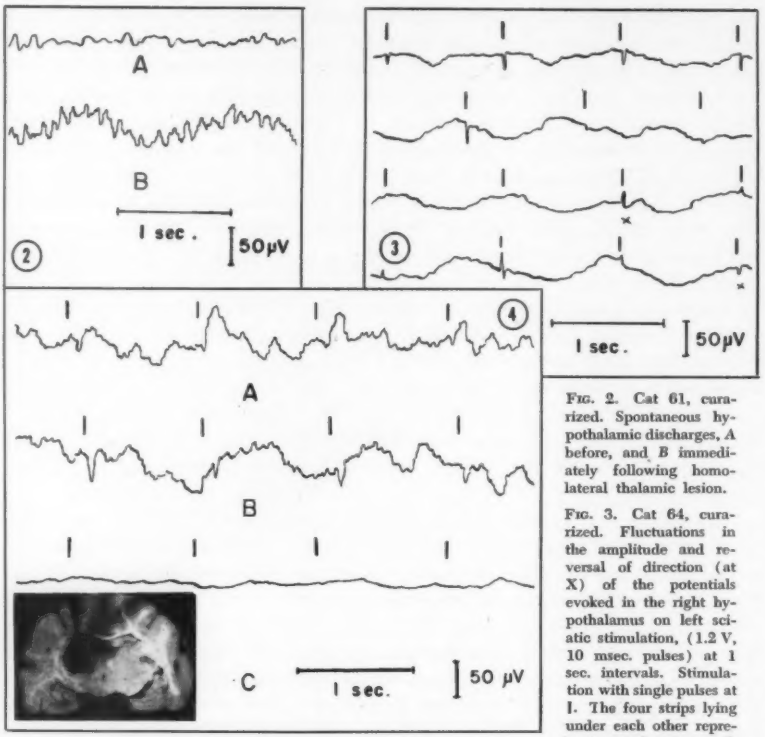



FIG. 2. Cat 61, curarized. Spontaneous hypothalamic discharges, *A* before, and *B* immediately following homolateral thalamic lesion.

FIG. 3. Cat 64, curarized. Fluctuations in the amplitude and reversal of direction (at X) of the potentials evoked in the right hypothalamus on left sciatic stimulation, (1.2 V, 10 msec. pulses) at 1 sec. intervals. Stimulation with single pulses at 1. The four strips lying under each other represent a continuous record.

FIG. 4. Cat 60, acute experiment. Electrical discharges of the left hypothalamus. *A* before thalamic lesion; *B* after lesion of the right nuclei ventral.posterior, lateral.posterior, lateral.posterior, pars intermedia, and pulvinar (inset); *C* control stimulation on dead animal. Left sciatic stimulation with single pulses at 1 (0.6 V, 10 msec. pulses).

tials which were not present or hardly demonstrable before the thalamic lesions appeared distinctly after such an injury.

The appearance of evoked potentials after the thalamic lesions may sometimes be due to the fact that the background activity of the hypothalamus is reduced by depression of the spontaneous hypothalamic discharges. However, it should be pointed out that this is not the only factor involved, and in some instances a definite increase of the amplitude of these evoked potentials could be demonstrated. Such changes could be found not only in the hypothalamus homolateral to but also in that contralateral to the side of the thalamic lesions. The hypothalamus opposite to the thalamic operation may even show a more marked increase of the evoked potentials than the ipsilateral hypothalamus, probably because depressor effects impair the vicinity of the lesion more than

the opposite side. Asymmetries of the reaction were, at least partly, due to asymmetric positions of the hypothalamic electrodes, for example, the electrode more distant from the midline failed to pick up evoked potentials.

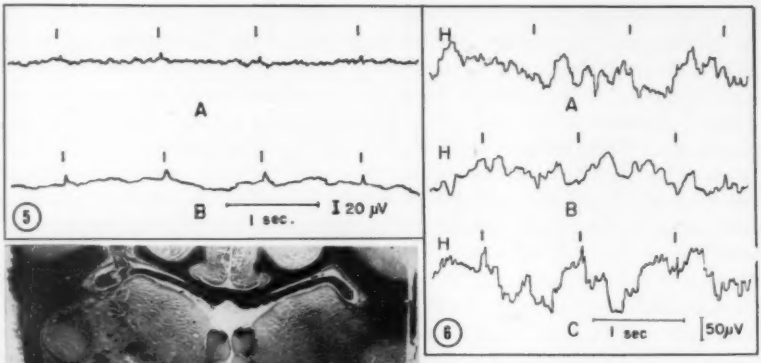
We have seen that disturbing factors were present in the acute experiments, depression as well as increase of hypothalamic activity. The former perhaps was due partly to the mechanical effect of the thalamic lesion or to the surrounding edema that affected particularly the ipsilateral hypothalamus, partly to loss of activating impulses from the thalamus to the hypothalamus. The hyperactivity could be due to the stimulating effects of the lesion upon the hypothalamus directly or upon neighboring thalamic cell groups that send facilitating impulses into the hypothalamus. It seemed desirable, therefore, to carry out a second series of experiments in which at least several days elapsed between the thalamic lesion and the hypothalamic recording. In general the results were quite similar for the evoked potentials; also in these experiments an increase of the evoked potentials as compared to the preoperative records could be observed (figure 5). There were also instances in which evoked potentials were hardly detectable in the hypothalamus before the thalamic lesion, but became clearly demonstrable after this operation (figures 6 and 7).

Regarding the spontaneous hypothalamic discharges, a stimulating effect of the thalamic lesion could be observed for as long as three days only. A permanent increase of the spontaneous activity could not be found. In contrast, a depression of the spontaneous discharges was observed not only immediately following the lesion. There also developed following a postoperative period with definite spontaneous hypothalamic activity, in the further course of observation, a decrease of the spontaneous hypothalamic potentials for which probably scar formation, chiefly glia proliferation around the electrode, was responsible. These depressor influences may explain why an increase of the evoked potentials could be found in only a part of the experiments, so that the positive cases with increased potentials would seem to be more significant for our problem than the negative ones in which such an effect could not be observed.

Definite signs of a release of the hypothalamus from thalamic inhibition could not be demonstrated. Also in a further series of 13 experiments in which the excitability of the hypothalamic pupillodilator center was compared before and after lesions of the ventral posterolateral nuclei, there were no indications of a release of the hypothalamus.

## DISCUSSION

The enhancement of evoked hypothalamic potentials after elimination of the ventral posterolateral nuclei may be explained most simply by assuming that the blockage of the endings of the ascending pathways in the ventral posterior nuclei by the lesion causes an increased number of afferent impulses to be diverted to the hypothalamus via bypaths which are normally only accessory routes. In this connection it may be recalled that, according to Eccles,[30a]



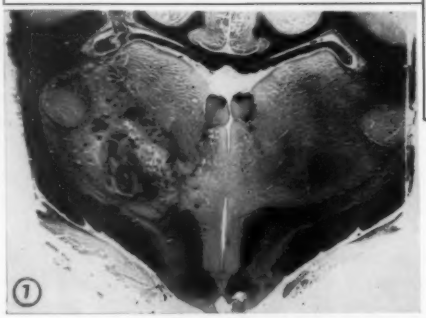




FIG. 5. Hypothalamic electrograms in unanesthetized cat. *A* before, and *B* three days after lesion of right ventral thalamic nuclei. I stimulation of left sciatic nerve with single pulses (4 V, 2 msec.)

FIG. 6. Electrograms of the left hypothalamus. *A* preoperative records (unanesthetized cat), and *B* immediately after thalamic lesion (see figure 7). Nembutal anesthesia. *C* one day postoperatively. Unanesthetized animal. Sciatic stimulation with single pulses (4 V, 2 msec.) at I.

FIG. 7. Thalamic lesion, corresponding to record in figure 6, involving chiefly the right ventral posterior nuclei.

the excitatory efficacy of the synaptic knobs of any one neuron is related to its usage.

Our experiments, which demonstrate an enhanced response of the hypothalamus to afferent impulses following lesions of the ventral posterior nuclei, are supplemented by clinical observations showing the importance of centripetal impulses in the genesis of the Dejerine-Roussy syndrome. If one succeeds in interrupting afferent pathways in the midbrain sufficiently so that a definite reduction of pain sensation results, relief from thalamic pain may be obtained.[15] With the return of pain conduction, probably due to increased use of remaining accessory pathways, the thalamic pain may more or less reappear. Similarly Frazier, Lewy, and Rowe[31] observed that bilateral cervical chordotomy combined with section of the trigeminal nerves relieved thalamic pain, at least transitorily.

Pain impulses may reach the higher centers after elimination of the ventral thalamic nuclei by various routes; chains of short neurons and the spinotectal system should be considered. As to the former, Schiff,[32] and Karplus and Kreidl[33] have shown, in experiments with crossed hemisections of the spinal cord, the importance of neuron chains crossing and synapsing in the gray matter around the central canal. Our own observations[34] have led to similar conclusions for impulses from the viscera, also when extraspinal conduction

could be excluded.[35] The importance of the reticular system has been stressed by Wallenberg[13] as early as 1928. A large part of the fibers ascending in the ventrolateral funiculus end in the oblongata and pons in the reticular formation (Foerster and Gagel[36] in man, Morin, Schwartz and O'Leary[37] in the monkey, Morin[38] in the cat). This spinal reticular system seems to be continued by reticulothalamic fibers that ascend in the medial area of the midbrain tegmentum toward the subthalamus and the centromedian nucleus of the thalamus.[38] By the study of potentials evoked by somatic and auditory stimulation, a rich supply of collateral connections to the midbrain tegmentum, subthalamus, and hypothalamus could be demonstrated,[21,21a] and desynchronization of the subthalamus and hypothalamus could be induced by reticular stimulation.[39] Further studies will have to elucidate to what extent one deals here with collaterals of long fiber systems, for example, of the medial lemniscus and of the spinothalamic and reticulothalamic system, and to what extent one deals with chains of short neurons.

Regarding the spinotectal system, observations may be of interest in patients in whom stereotaxically oriented bipolar electrodes were inserted in the midbrain under local anesthesia for operative purposes. Stimulation of the region of the tectum mesencephali produced a pain sensation that was localized in the opposite side.[40] The exact position of the electrodes could obviously not be checked by anatomic examination, and the level of the stimulating points could only be estimated from roentgenographic measurements. It was surmised that one of the areas from which pain reactions were elicited corresponded to the mesencephalic projections of the spinotectal tract. An analysis of these observations in animal experiments[41] showed that on electric stimulation pain suggestive reactions (crying, struggling, flight reactions) could be produced from the tectum mesencephali and were more readily elicited as one proceeded from the anterior to the posterior corpora quadrigemina. Not only electrical but also mechanical stimulation of the periaqueductal gray matter was able to elicit crying, snarling, and defense reactions. In the midbrain tegmentum not only the long sensory systems but also dorsal and ventral parts of the reticulate substance yielded pain suggestive reactions.

The possibility that a lowest level of integration of pain may exist at the mesencephalic level, chiefly in the tectum mesencephali, as has been assumed by Walker,[26] cannot be denied, particularly for the pain felt after destruction of the endings of the long pain conducting systems in the thalamus. In these cases, the entrance of pain impulses in the tectum may be important in determining the direction in which the pain is projected, since on tectal stimulation our patients felt the pain in the opposite side.[40] However, it seems that tectal integration of pain cannot sufficiently explain the effect of emotions upon the thalamic pain and its frequent association with vegetative disturbances. For these phenomena the integration of pain at the hypothalamic level seems to give a plausible explanation.

There are numerous pathways by which impulses may be conducted from

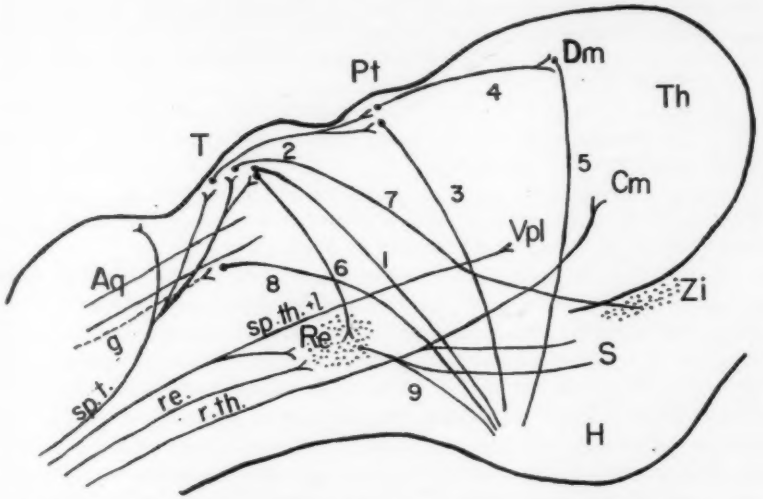



FIG. 8. Possible pathways for pain conduction into the hypothalamus. Aq=aqueduct; Cm=centre median; Dm=dorsomedial nucleus; g=possible conduction in periaqueductal gray matter; H=hypothalamus; Pt=pretectal region; Re=reticular nuclei; re=reticular pathways; rth=reticulothalamic tract; S=subthalamus; Sp.th.+l.=spinothalamic tract and medial lemniscus; T= tectum mesencephali; Th=thalamus; Vpl=ventral posterolateral nuclei; Zi=zona incerta. Numbers 1-9 are explained in the text.

the mesencephalon to the hypothalamus. They may be briefly summarized as follows (figure 8).

1. Connections from the tectum mesencephali to the hypothalamus.
   a) Direct connections:
      Tectohypothalamic fibers (Hines,[42] figure 8, No. 1).
   b) Indirect connections:
      1) Tectopretectal fibers (Rioch,[43] figure 8, No. 2) continued by systems originating in the pretectal nuclei.
         (a) periventricular fibers to the hypothalamus (Kuhlenbeck and Miller,[44] figure 8, No. 3).
         (b) fibers to the dorsomedial nuclei (Rioch,[43] figure 8, No. 4) and from here periventricular fibers to the hypothalamus (figure 8, No. 5).
      2) Tectoreticular fibers (Marburg and Warner,[45] figure 8, No. 6) continued by systems originating in the reticulate substance (see below).
      3) Fibers to the zona incerta (Bucher and Bürgi,[46] figure 8, No. 7); continuation to hypothalamus?
2. Fibers from the periaqueductal gray to the posterior hypothalamus (Bucher and Bürgi,[47] figure 8, No. 8). These fibers perhaps play a role in continuing the previously mentioned chains of neurons that cross and synapse in the gray matter around the central canal.

3. Reticulate substance. Neuron chains in the reticular substance and impulses entering it by way of collaterals of long systems are continued into the hypothalamus (figure 8, No. 9), for example, from the ventral tegmental nucleus via mammillary peduncle (Ibanez,[47a] Tello[47b]).

It should be emphasized that this diagram presents only anatomic pathways that may play a role in the conduction of pain impulses and other afferent impulses to the hypothalamus. To what extent these fiber systems participate in the conduction of such impulses still has to be analyzed. Lemniscal fibers carrying impulses from sacral segments and reaching the mammillary body along its peduncle were described by Wallenberg.[13]

By way of the hypothalamus or by activation of the diffuse thalamocortical projection system,[48,49] afferent impulses may reach the cerebral cortex after elimination of the thalamic endings of the long afferent systems. In the experiments of Spiegel and Szekely[50] it could be shown that isolation phenomena develop in the sensory cortex after lesions of the ventral posterolateral thalamic nuclei. After an initial diminution, the spontaneous electrical activity of the sensory cortex may not only return, but it may even increase in amplitude as compared to the unoperated side; periodic burst discharges may also appear. On bilateral stimulation of sensory nerves, the potentials (so-called secondary responses of Forbes and his associates[51]) evoked in the sensory cortex deprived of its connections with the ventral posterior thalamic nuclei show an equal or even slightly higher amplitude than on the unoperated side. The affected cortical area may develop a hypersensitivity to toxins such as Metrazol or Mecholyl. These drugs may accentuate an existing or bring to light a latent asymmetry of the spontaneous discharges and/or the tendency to burst discharges. These phenomena may play an accessory role in the mechanism of the thalamic syndrome. For instance, the cortical integration of the pain impulses may supplement the previously mentioned tectal integration in determining the direction of the pain sensation. But the cortex is not essential for the genesis of the thalamic hyperpathia since this phenomenon persists after ablation of the sensory cortex, as is evident also in our material. The development of supersensitivity in the sensory cortex after its afferent impulses from the ventral posterior thalamic nuclei have been cut off may be important for the development of pain and hyperpathia in another group of cases, that is, in certain cerebral lesions that extend into the white matter below the sensory cortex.[10]

Variations in the extent of the thalamic lesions may modify the pathogenetic mechanisms outlined in this paper. In small lesions of the ventral posterior nuclei, the impulses blocked by the lesion may flow not only toward the hypothalamus but also toward cell groups of the ventral nuclei in the vicinity of the lesion, along normally less used collaterals; this may explain the hyperpathia of parts of the body adjacent to the hypesthetic part observed by Monnier[52] following coagulation of small circumscribed foci of the ven-

tral posterior nuclei.* Large lesions extending toward and encroaching upon the cerebral peduncle may prevent the entrance of centripetal impulses into the hypothalamus as we could observe in some of our experiments.

It is also possible that nuclei or fiber systems in the vicinity of the ventral posterior nuclei are able to modify the mechanism analyzed by our experiments; for instance, in some of our observations lesions affecting cell groups dorsal to the ventral posterior nuclei increased the electric activity of the hypothalamus. An experimental study of such additional factors is under consideration.

SUMMARY

1. For the development of thalamic pain ascending impulses entering the diencephalon are essential, since the thalamic pain disappears if the ascending systems passing through the midbrain are interrupted in sufficient extent so that a definite hypalgesia results.

2. After elimination of the endings of the long afferent systems in the ventral posterior thalamic nuclei, there are three areas where pain impulses may be integrated: in the mesencephalon, particularly its tectum, in the hypothalamus, and in the cortex.

3. The sensory cortex develops isolation phenomena following lesion of the ventral posterior nuclei but seems to play only an accessory role in the development of the thalamic syndrome, since its ablation does not abolish the thalamic pain. The cortical and mesencephalic integration of the pain impulses may play a part in determining the localization of the pain, but also its tectal origin does not sufficiently explain certain features of the thalamic pain such as its response to emotions and the associated vegetative disturbances.

4. It is, therefore, suggested that the entrance of pain conducting impulses into the hypothalamus plays an important role in the genesis of the Dejerine-Roussy syndrome. This view is supported by experiments showing that elimination of the ventral posterior thalamic nuclei is able to increase the potentials evoked in the hypothalamus by stimulation of afferent nerves.

*The existence of such collaterals is suggested by the experience of Dusser de Barenne and Sager[53] with localized injections of small amounts of strychnine into thalamic nuclei. They found that strychninization of a thalamic nucleus as a rule affected two body areas (for example, head, arm) simultaneously and concluded that the functional (somatotopic) localization in the thalamus is much less sharp than in the cerebral cortex. Monnier explains his observations by assuming that the thalamus contains an apparatus that favors the irradiation of pain impulses. This explanation does not consider the fact that the hyperpathia of adjacent areas developing after circumscribed coagulation is a pathologic phenomenon appearing some time after the operation, but that such an irradiation is not present when the thalamus is intact and functions normally. Monnier's therapeutic experiments are important in two respects: they show again that a circumscribed lesion of the ventral thalamic nuclei induces hyperpathia and they confirm our view that operative procedures on the thalamus should avoid the area of those nuclei.

We should like to express our appreciation to Dr. W. P. Chapman and Dr. J. M. Delgado for recommending the type of wire electrodes used in these experiments.

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# Clinical Evaluation of Focal Depression of Voltage in Electroencephalography

*Walter J. Friedlander, M.D.*

FOCAL DEPRESSION OF VOLTAGE in electroencephalograms has been noted to occur in numerous pathologic conditions. Invariably the studies concerning this began with the pathology already known to the investigator who then correlated the associated electroencephalographic findings. In the clinic, however, the situation is just the opposite, that is, the electroencephalographer has a given record and from that he attempts to draw conclusions about the presence, location, and perhaps the type of cerebral pathology. However, the most valuable way to judge the clinical value of this or any other electroencephalographic pattern is to study a statistically significant series of records and then correlate these findings with the clinical findings. It is perhaps insufficient to use normal controls to evaluate a particular electroencephalographic finding because they do not accurately represent the population that the electroencephalographer has in his clinic.

We have posed the question, "What is the clinical usefulness of focal depression of amplitude in the electroencephalogram?" To answer this we have reviewed a statistically significant series of records obtained from the same type of population that we examine in our electroencephalographic laboratory. Except for certain qualifications which will be discussed later, our conclusions are felt to be valid for our population, but perhaps valid only within certain limits for any other group. Because of this a detailed description of our particular population is indicated.

Our laboratory serves a 440 bed general medical and surgical hospital. Among the various residency training programs is one in neurology and another in neurosurgery. The neurology section makes up 5 per cent of the total hospital beds; the psychiatric section also has 5 per cent of the beds. The senior neurology staff is particularly interested in the electroencephalographic findings which might account for a greater number of referrals than would normally be expected. There is no out-patient clinic but there are outpatient facilities for follow-up investigation. The age distribution of the patients studied is shown in figure 1; the average age was 40.7 years, with the range from 20 to 86 years. Records were obtained on a Grass model III-C electroencephalograph using a 16 needle electrode placement. The placement of electrodes is shown in figure 2. The reference electrode in monopolar runs

From the neurology section of the Veterans Administration Hospital, San Francisco.

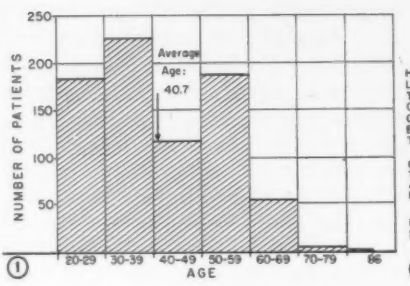


FIG. 1. Age distribution of patients in the series.

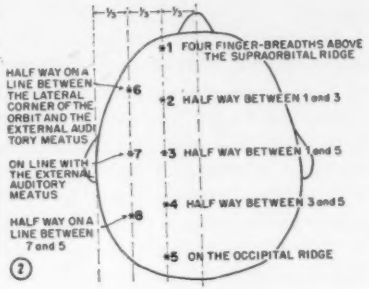
1/3
1/3
1/3
#1 FOUR FINGER-BREADTHS ABOVE THE SUPRAORBITAL RIDGE
#2 HALF WAY BETWEEN 1 and 3
#3 HALF WAY BETWEEN 1 and 5
#4 HALF WAY BETWEEN 3 and 5
#5 ON THE OCCIPITAL RIDGE
#6
#7
#8
HALF WAY ON A LINE BETWEEN THE LATERAL CORNER OF THE ORBIT AND THE EXTERNAL AUDITORY MEATUS
ON LINE WITH THE EXTERNAL AUDITORY MEATUS
HALF WAY ON A LINE BETWEEN 7 and 5
2

FIG. 2. Placement of the electrodes.

was obtained by connecting electrodes from each ear lobe. Control runs indicated that variation of placement of the electrodes within at least 1 cm. did not produce any difference in recorded voltage. The hyperventilation portion of each record has not been included in this particular study. All the patients were supine, resting, but awake.

A total of 1,010 consecutive records obtained from 774 patients were reviewed. Focal depression of amplitude was classified as minimal, moderate, or marked. Minimal depression was defined as a slight but definite decrease in amplitude occurring in at least 75 per cent of a two minute run; frequently there were small portions of the run in which the amplitude asymmetry was absent. Moderate depression was characterized by a greater amount of depression of voltage and marked depression by an extreme amount of depression; both of these degrees of depression were present during the entire two minute run. If there was an amplitude asymmetry because the voltage on one side was increased, the contralateral apparent depression of amplitude was not considered real and therefore was not included in our series. The clinical charts of those who had greater than minimal depression of voltage were reviewed. In all patients, evidence of focal pathology obtained from the chart included a history, a neurologic examination, and electroencephalographic findings (other than amplitude asymmetries). Most patients also had skull roentgenograms and pneumoencephalograms, and in some cases angiograms, ventriculograms, surgery, or postmortem examinations were performed.

## FINDINGS

Only minimal focal depression of voltage was found in the records of 168 patients or 22 per cent of the entire series. Its distribution is noted in figure 3. More than one record was obtained in 36 of these patients, and only 17 or 47 per cent showed *some* degree of focal decrease in amplitude on the same side in more than one record. Distribution of these and their correspondence with the *laterality* of the clinical focal pathology is diagrammed in figure 4.

Moderate or marked degrees of focal depression of voltage were seen in the records of 93 patients or 12 per cent of the entire series. Of these, 53

patients, 56 per cent of all those with greater than minimal depression and 7 per cent of the entire series, had focal depression of voltage without any corresponding alteration of rhythm (FD, figure 5); 40 patients, 43 per cent of those with greater than minimal depression and 5 per cent of the entire series, had focal depression of voltage with some alteration of rhythm (FDA, figure 6). The correspondence or lack of correspondence of these findings with the *laterality* of the clinical focal pathology is summarized in table 1. The relation between focal depression of voltage noted in bipolar, monopolar, and both bipolar and monopolar runs and the clinical findings are summarized in table 2. There were only 12 patients who had a marked degree of FDA; this represents 1.6 per cent of the entire series and 13 per cent of all those with more than a minimal degree of focal depression of voltage. In the marked FDA group there were 83 per cent true positives, as compared with 63 per cent true positives in the moderate FHD group and 70 per cent in the total greater than minimal depression FDA group. The type of pathology found in those patients who had more than a minimal amount of focal depression on the same side as the clinical pathology is listed in table 3.

### CRITICISM OF TECHNIC

There are three weaknesses in our methodology: 1) the means of deciding whether there is an ipsolateral focal depression of voltage or a contralateral increase in voltage, 2) indefiniteness of classification of the degree of depression of voltage, and 3) the reliability of the presence and location of an area of focal brain pathology based on clinical examination only.

In most cases there was no difficulty deciding whether there was an ipsolateral focal decrease or a contralateral focal increase in voltage. Where there was a serious question about this, even after the records were reviewed several times, we attempted to err on the conservative side and regarded these records as examples of *no* focal depression of voltage.

As for groupings, a simple three point scale was decided upon after several attempts at using a more exact classification. Such a scale is comparable to the three point scale of normal, borderline, and abnormal commonly used in electroencephalography. Except where the decrease in the voltage is of such a marked degree that the recording is almost a simple straight line, there is so much variation of the amplitude in a two minute recording that the only exact way of arriving at an average is to employ some planimetric method. Since the question we originally posed concerned the usefulness of focal decrease of voltage in the clinic and planimetric methods are very time consuming, the use of such a scheme would not help in answering our specific question.

Though the presence and location of focal brain pathology was determined by anatomic inspection of the brain occasionally, in most cases the conclusions were based on clinical examination only. It is impossible to limit all our cases to those who had either surgery or came to autopsy since this would limit the pathology to those conditions treated by surgery and/or those

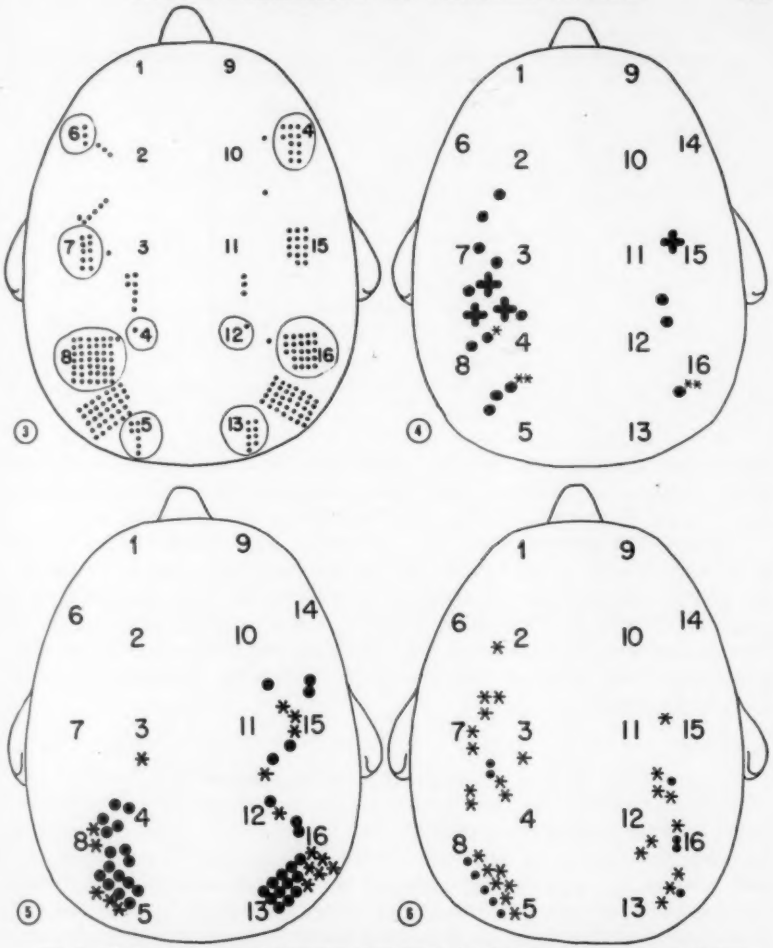


FIG. 3. Distribution of minimal depression of voltage in the electroencephalogram where 1) there was no associated decrease in potential of any more severe degree in the same record and 2) in records where both monopolar and bipolar recordings were obtained; if minimal decrease in voltage was seen in the same location in more than one record, it is recorded only once. Dots within the encircled areas represent monopolar recordings and those outside the encircled areas represent bipolar recordings.

FIG. 4. Correspondency (+) or lack of correspondency (●) of decreased voltage and clinical evidence of focal pathology on the same side in serial electroencephalograms in which a minimal depression of voltage was seen in one record and some degree of depression of voltage was seen in the same area in at least one other record. *—no clinical focal pathology found; **—no clinical pathology found (two records had minimal depression of voltage in leads 5, 8, and 5-8, and two records had minimal decrease depression of voltage in leads 13 and 13-16).

FIG. 5. Distribution of moderate or marked degree of FD. (*) FD corresponds correctly with side of clinical focal pathology; (●) FD does not correspond correctly with side of clinical pathology or there was no clinical evidence of focal pathology.

FIG. 6. Distribution of moderate or marked degree of FDA. (*) FDA corresponds correctly with side of clinical focal pathology; (●) FDA does not correspond correctly with side of clinical pathology or there was no clinical evidence of focal pathology.

TABLE 1

CORRELATION BETWEEN ELECTROENCEPHALOGRAPHIC FINDINGS AND LATERALITY OF CLINICAL FOCAL PATHOLOGY

| EEG FINDING | | NUMBER* OF PATIENTS | % | % | |
|---|---|---|---|---|---|
| FD | CORRECT LATERALIZATION | 7 | 13 | 34 | |
| | QUESTIONABLY CORRECT LATERALIZAT'N | 11 | 21 | | |
| | INCORRECT LATERALIZATION | 3 | 6 | 23 | 66 |
| | QUESTIONABLY INCORRECT LATERALIZ'N | 9 | 17 | | |
| | NO EVIDENCE OF FOCAL PATHOLOGY | 23 | 43 | 43 | |
| FDA | CORRECT LATERALIZATION | 22 | 55 | 70 | |
| | QUESTIONABLY CORRECT LATERALIZAT'N | 6 | 15 | | |
| | INCORRECT LATERALIZATION | 3 | 8 | 20 | 30 |
| | QUESTIONABLY INCORRECT LATERALIZ'N | 5 | 13 | | |
| | NO EVIDENCE OF FOCAL PATHOLOGY | 4 | 10 | 10 | |

*12% of the entire project.

that had a fatal outcome within a reasonably short time after an electroencephalogram was obtained. Also, some degree of flexibility regarding certainty of the focal pathology has been included in our groupings.

There will certainly be those who will raise a point that just because there is no clinical evidence of focal pathology does not mean that the focal depression of voltage is not a measure of some localized brain abnormality not otherwise delineated. There is no answer to this except to qualify our initial question and now ask, "How well does focal depression of voltage in the electroencephalogram correlate with the laterality of other clinical evidence of focal brain pathology?"

## DISCUSSION

Many authors refer to the appearance of focal depression of voltage and describe it as "silent area," "quiescent area," "area of extinction," "suppression," "quiet," "depression of basic rhythm," or "hypopotentia." There have been several papers devoted to "amplitude asymmetry," but these do not specifically note whether one side has depressed voltage or its homologue on the other side has increased voltage. With the exception of the paper by Williams and Rynell,[1] no report has been found that sets out to evaluate this single phenomenon, focal voltage depression.

There have been relatively few studies of the incidence of amplitude asymmetry in normals. Using bipolar recordings, Williams and Reynell[1] found no significant asymmetries in 355 normals. Sugar[2] found amplitude asymmetries in the occipital area in only 11.5 per cent of 26 normal adults. On the other hand Raney[3] and Cornil and Gastaut[4] reported larger numbers of normals who have some degree of amplitude asymmetry. Raney found, in 34 normals, a difference of voltage of greater than 5 per cent in 88 per cent of the leads from central areas and 91 per cent from the occipital areas. Cornil and Gastaut, having examined 120 adults and 30 children between the ages of five

TABLE 2

CORRELATION BETWEEN ELECTROCARDIOGRAPHIC FINDINGS IN BIPOLAR, MONOPOLAR, AND BIPOLAR AND MONOPOLAR RUNS AND LATERALITY OF CLINICAL FOCAL PATHOLOGY

| TECHNIQUE | | EEG FINDING | NUMBER OF PATIENTS | % | % | % OF TOTAL BIPOLAR OR MONOPOLAR FHA |
|---|---|---|---|---|---|---|
| BIPOLAR* | CORRECT, OR QUESTIONABLY CORRECT LATERALIZATION. | FD | 13 | 21 | 45 | |
| | | FDA | 15 | 24 | | 71 |
| | INCORRECT, QUESTIONABLY INCORRECT, OR NO FOCAL PATHOLOGY. | FD | 30 | 48 | 56 | |
| | | FDA | 6 | 6 | | 29 |
| MONOPOLAR* | CORRECT, OR QUESTIONABLY CORRECT LATERALIZATION. | FD | 7 | 20 | 51 | |
| | | FDA | 11 | 31 | | 64 |
| | INCORRECT, QUESTIONABLY INCORRECT, OR NO FOCAL PATHOLOGY. | FD | 11 | 31 | 49 | |
| | | FDA | 6 | 17 | | 35 |

*If focal hypotentia was seen in both bipolar and monopolar runs it has been included in both.

| | | | |
|---|---|---|---|
| BIPOLAR and MONOPOLAR | CORRECT OR QUESTIONABLY CORRECT LATERALIZATION | FD | 3 |
| | | FDA | 4* |
| | INCORRECT, QUESTIONABLY INCORRECT, OR NO FOCAL PATHOLOGY | FD | 5 |
| | | FDA | 0 |

*These 4 patients represent 0.5% of the entire project.

and 12 years, reported amplitude asymmetries in more than one-half with the dominant side usually lower. Aird and Zealear[5] found differences in homologous potentials in 13 per cent of normal electroencephalograms. Earlier Aird and Bowditch[6] commented more specifically that the temporal and occipital areas were the most common sites of bilaterally unequal potentials in normals. Strauss, Liberson, and Meltzer[7] described an "index of asymmetry" which was the percentage alpha time in the hemisphere with the greatest alpha divided by the percentage alpha time in the other hemisphere. It can probably be assumed that in normals the alpha percentage was inversely proportionate to the amplitude. If this is so, these authors reported that in right-handed normals, some voltage asymmetry (index of asymmetry of 1.1) was present in the parietal area in 30 per cent and in the occipital area in 14 per cent. A somewhat greater asymmetry (index of asymmetry of 1.2) was found in the

TABLE 3

TYPE OF PATHOLOGY IN PATIENTS WHO HAD A CORRECT CORRELATION BETWEEN LATERALITY OF CLINICAL PATHOLOGY AND GREATER-THAN-MINIMAL FOCAL DEPRESSION OF ELECTROENCEPHALOGRAPHIC VOLTAGE

| DIAGNOSIS | FD | | FDA | | TOTAL |
|---|---|---|---|---|---|
| | CORRECT LOCALIZATION | QUESTIONABLE CORRECT LOCALIZATION | CORRECT LOCALIZATION | QUESTIONABLE CORRECT LOCALIZATION | |
| **VASCULAR DISEASE** | | | | | 10 |
| Cerebral arteriosclerosis with epilepsy | | | 1 | | (1) |
| Cerebral artery thrombosis | | | 5 | | (5) |
| Hypertensive encephalopathy | | | 1 | 1 | (2) |
| Spontaneous subarachnoid hemorrhage | | | 1 | 1 | (2) |
| **NEOPLASMS** | | | | | 7 |
| Metastatic to brain | 1 | | 1 | | (2) |
| Astrocytoma | | | 2 | | (2) |
| Meningioma | | | 1 | | (1) |
| Ependymoma | | | 1 | | (1) |
| Suspected | 1 | | | | (1) |
| **INFECTION** | | | | | 5 |
| Tertiary CNS lues | 2 | | | | (2) |
| Encephalitis, acute (herpes) | | 1 | | | (1) |
| Meningitis, probably bacterial, subacute | | 1 | | | (1) |
| Encephalitis, history of | | | | 1 | (1) |
| **TRAUMA** | | | | | 8 |
| Epilepsy, symptomatic, due to trauma | 1 | | 1 | | (2) |
| History of repeated head trauma | | 1 | 1 | | (2) |
| Birth trauma with unilat. cortical atrophy | | | 1 | | (1) |
| Encephalopathy due to trauma | | 1 | 2 | | (3) |
| **EPILEPSY** symptomatic, etiology undetermd | 1 | | 3 | 3 | 7 |
| **BRAIN ATROPHY** etiology undetermined | 1 | 2 | | | 3 |
| **MULTIPLE SCLEROSIS** | | 2 | 1 | | 3 |
| **PARKINSONISM** | | 1 | | | 1 |
| **CNS DISEASE** etiology undetermined | | 1 | 1 | | 2 |

parietal area in 20 per cent, and in the occipital area in 7 to 10 per cent of their cases.

Jasper, Fitzpatrick, and Solomon[8] using bipolar and monopolar studies found "marked differences" in the amplitude of the electrical activity from homologous head regions in 25 per cent of schizophrenic patients. No other reports have been found which specifically mention potential differences in non-organic psychiatric conditions, except for Williams and Reynell[1] who noted that there may be an abnormal amount of asymmetry in various kinds of behavior disorders on rare occasions.

Numerous papers from different laboratories have made general statements regarding the value of focal depression of voltage. Case and Bucy[9] listed among their localizing signs "marked diminution or absence of electrical activity." Strauss[10] stated that among the "most important signs of focal pathology is depression of normal activity on one side." Courville[11] felt that "quiescence of rhythm is almost as valuable a localizing sign as is slow activity." Williams and Reynell found "silent areas" in a number of pathologic conditions. Rohmer, Gastaut, and Dell[12] listed several pathologic central nerv-

ous system conditions where "depression of basic rhythm" aided in localization. Busse and Dale,[13] in discussing the value of electroencephalography in clinical medicine, indicated that areas of "electrical quiescence" may be of diagnostic value. Spillane[14] and Ward[15] have described focal depression of voltage as being of some value. Gibbs[16] also believes that "decreased voltage production is one of the evidences of brain damage."

More specifically, focal depression of voltage in the electroencephalogram has been reported in subdural or epidural hematomata or hydromata, cerebral vascular accidents, aneurysm formation, brain injury, brain atrophy, porencephaly, cerebral palsy, tumors, abscesses, migraine, and even after Diodrast angiography.[17] It is this rather formidable list of types of central nervous system pathology which emphasizes the fact that a focal decrease in amplitude is not pathognomonic of any specific condition.

To further illustrate this, we have culled from the literature 330 cases of subdural hematoma in which the electroencephalographic findings were given in a fair amount of detail.[1,18–45] Some of these are single case reports which might bias any statistical evaluation of the whole group; also some authors do not clarify their findings about particular electroencephalographic abnormalities. However, the following data were obtained from this series: 85 per cent had signs which at least partially correctly localized the subdural; only 51 per cent had electroencephalograms which had a noteworthy degree of focal decrease in amplitude on the correct side; and 12 per cent had normal records.

In summary, there is a general consensus that focal decrease in the voltage suggests "dead" or at least functionally inactive cells, in contrast to slow activity which implies "sick" cells. Further, the work of Murphy and Dusser de Barenne[47] suggests that it is the more specific involvement of the deep layers of the cortex which produces depression of voltage.

Hence, there is no doubt that certain pathologic conditions will manifest themselves as lowered voltage in the electroencephalogram. However, this is approaching the problem from just the opposite direction than the clinical electroencephalographer does when he attempts to draw conclusions about a given record. Starting now with the electroencephalogram and working back to the clinical pathology, we believe we can answer the question initially posed with at least the relative statement that there is some correlation between the side of the clinically demonstrable focal pathology and the focal decrease in voltage of the electroencephalogram when this is associated with an alteration of rhythm. There is, too, the suggestion of a negative correlation if only FD is observed. The percentage of "true positives" increases in the following circumstances: 1) the more anterior the focus, 2) the greater the amount of voltage depression, and 3) the presence of FDA occurring in both monopolar and bipolar runs. All three of these findings, however, are rare; in fact, FDA in both monopolar and bipolar runs, which had a 100 per cent correlation with the laterality of the focal clinical pathology, is so rare that the "n" in our series is probably too small to allow any definite conclusions. Also, there appears to be no good correlation between the type of pa-

thology and the occurrence of focal decrease in voltage. Since the brains of most of the patients in our series were not examined anatomically, it is impossible to reach any conclusions about the correlation between the location in regard to depth of the pathology and the occurrence of this particular phenomenon in the electroencephalogram.

SUMMARY

A series of 1,010 electroencephalograms obtained on 774 patients were reviewed for the presence and degree of focal decrease in voltage. The clinical findings of those having moderate or marked degrees of decrease in voltage were then investigated.

There is a suggestion of a statistical correlation between the side of demonstrable focal pathology and focal decrease in amplitude with associated alteration of rhythm, but this is not very great.

The circumstances that increase the percentage of "true positives" have been indicated.

There appears to be no good correlation between the type of pathology and the occurrence of focal decrease in electroencephalographic potential either in this series or from a review of the literature.

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The faculties of the mind have been called very happily, internal senses. They resemble the external senses in being innate, and depending wholly upon bodily impressions to produce their specific operations. These impressions are made through the medium of the external senses. As well might we attempt to excite thought in a piece of marble by striking it with our hand, as expect to produce a single operation of the mind in a person deprived of the external senses of touch, seeing, hearing, taste and smell.

All the operations in the mind are the effects of motions previously excited in the brain, and every idea and thought appears to depend upon a motion peculiar to itself. In a sound state of mind these motions are regular, and succeed impressions upon the brain with the same certainty and uniformity that perceptions succeed impressions upon the senses in their sound state.

Benjamin Rush in *Medical Inquiries and Observations upon the Diseases of the Mind*, published in 1812.

# Mestinon in the Treatment of Myasthenia Gravis

*Martha R. Westerberg, M.D.*
*and Kenneth R. Magee, M.D.*

PRIOR TO THE INTRODUCTION OF NEOSTIGMINE by Walker in 1935,[1] there was no satisfactory treatment for myasthenia gravis. Ephedrine was helpful but inadequate for the majority of patients. Since the therapeutic effect of neostigmine in myasthenia gravis was discovered, it has been the drug of choice for the treatment of this disorder. The organic phosphates have been evaluated and though very helpful in certain cases, they usually cannot replace the patient's full neostigmine dose, and experience with them is necessary because of hazards inherent in their use. Likewise, Tensilon was recently evaluated and found to be very effective in alleviating the myasthenic symptoms.[2] However, this effect is obtained with intravenous injection and is transitory, while oral ingestion of Tensilon is relatively ineffective. Therefore, aside from its use as a diagnostic agent,[3] Tensilon is of little value in the day by day management of myasthenia gravis.

Despite its unchallenged position in the therapy of myasthenia gravis, neostigmine has several obvious disadvantages. First, the effect is present for only a few hours at most, necessitating the ingestion of great quantities of medicine each day in the more severe cases. Aside from the expense of the medication and the inconvenience, this would be no great handicap except that many patients claim that they experience a feeling of being let-down after having taken the drug a few hours before. This let-down feeling occurs rather suddenly and does not give the patient sufficient time to get more neostigmine into his system. This seems to occur only in certain patients, but when it does it is quite annoying. Secondly, the autonomic side effects of neostigmine are often troublesome and, despite covering doses of atropine, they may hinder treatment.

Thus it is evident that a compound without these disadvantages would benefit the myasthenic patient. Recently, a cholinergic drug homologous to neostigmine has been developed. It is most commonly known as Pyridostigmin or Mestinon. Pyridostigmin or Mestinon has been known since 1947 and previous clinical reports concerning its use have been published.[4,5,6] Its use,

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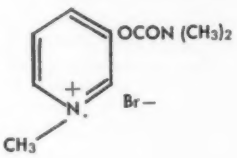
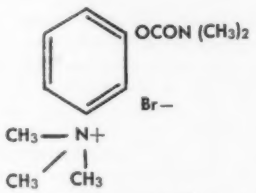
however, has been limited in this country, and for this reason it seems worthwhile to report its evaluation in a series of 22 unselected patients with myasthenia gravis.

CHEMISTRY AND PHARMACOLOGY

Mestinon bromide is an analogue of neostigmine bromide. It is the dimethyl carbamic ester of 3-hydroxy-1-methylpyridinium bromide. Neostigmine bromide is the dimethyl carbamic ester of 3-hydroxy phenyltrimethylammonium bromide. The structural formulas are compared below.




Mestinon bromide




Neostigmine bromide

Mestinon is available in 60 mg. tablets and ampuls of 5 cc. containing 2 mg./cc. It is relatively nontoxic. The acute toxicity as expressed by the $LD_{50}$ in mg./kg. in mice by intravenous injection is 1.5 for Mestinon as compared with 0.16 for neostigmine. By subcutaneous injection the $LD_{50}$ for Mestinon is 2.7 while the oral $LD_{50}$ is 32.0. Similar figures for neostigmine are 0.42 and 7.5, respectively, approximately one-fifth that of Mestinon. Therapeutic dosages are found experimentally to cause no significant changes in arterial blood pressure. The action of Mestinon on isolated strips of rabbit jejunum is one-eighth that of neostigmine. The anticurare action of Mestinon on neuromuscular transmission in dogs and cats is approximately one-fourth that of neostigmine. Miotic action is moderate at 0.5 per cent for Mestinon and pronounced at the same concentration of neostigmine. The anticholinesterase activity measured by the Warburg technic on purified eel esterase is 1 per cent that of neostigmine. It is evident that Mestinon is approximately one-half to one-fourth as strong but one-fifth as toxic as neostigmine. General detailed reports regarding the chemical and pharmacologic data have been published.[7–15]

CLINICAL EVALUATION

A total of 22 patients were evaluated in this study. All patients were taking neostigmine when Mestinon was substituted abruptly. Most patients were taking adjuvant drugs including ephedrine, potassium, and tetraethylpyrophosphate. Many patients also required the use of atropine sulfate tablets. The adjuvants were continued while Mestinon was taken. All patients were then asked to stop Mestinon and substitute neostigmine for a week, so that the factor of spontaneous change in the patient's course would not influence

their evaluation. All patients were examined before and during therapy but the patients' subjective responses were recorded by them for the study. The difference in physical size of the two tablets made it impossible to substitute one for the other without the patient's knowledge.

CASE REPORTS

*Case 1.*—An 18 year old schoolgirl developed typical myasthenia gravis following a respiratory infection in March 1953. Mild generalized weakness and diplopia were present, but the major disability was dysarthria and dysphagia. Neostigmine bromide, 30 mg. every waking hour, gave moderate relief but the dysarthria remained severe. On February 1, 1954, she was instructed to discontinue neostigmine and begin taking Mestinon in 60 mg. tablets as needed. She has followed this program to the present time, stating that she definitely prefers Mestinon to neostigmine. The patient claims that Mestinon will take effect in 15 minutes as compared with 45 to 60 minutes for neostigmine, and the effect will last three to four hours as compared with one hour for neostigmine. She finds that 120 mg. of Mestinon every two hours gives best results and increases her strength considerably above the level obtained with 30 mg. of neostigmine every hour. All muscles are stronger, the most noticeable effect from the patient's point of view being the improvement in her voice and swallowing. She also states that the muscles in her face feel more relaxed. The patient's appetite has improved and she has begun to gain weight. Reexamination confirmed the improvement, particularly in her speech, which is much clearer than when she was taking neostigmine alone. The patient noted abdominal cramps when taking neostigmine in therapeutic doses. There were no side reactions with Mestinon. On request the patient discontinued Mestinon and returned to neostigmine, but in three days noted such marked deterioration that she returned to Mestinon, again noting prompt improvement.

*Case 2.*—A 30 year old housewife developed myasthenia gravis in December 1950. Diplopia and weakness of the upper extremities were the most severe complaints. She had been doing well on an average of 150 mg. of neostigmine daily, along with potassium citrate. The patient was very tense and mild relapses seemed to coincide with periods of increased tension, which could often be relieved with phenobarbital. Occasionally the patient noted mild diarrhea from neostigmine, but there were no serious side effects from the maintenance dose.

In January 1954 the patient was advised to substitute 60 mg. tablets of Mestinon for neostigmine. Otherwise no change was made in her program. Within a day after beginning Mestinon and after taking about five tablets, the patient stated she began to feel "terrible." Diplopia returned and she noted general weakness, dizziness and nervousness, hot and cold sensations in her extremities, numbness of her extremities, limpness of legs, and many other complaints. She stated that Mestinon acted about as fast and lasted about as long as neostigmine, but aside from waking in the morning a little stronger than when taking neostigmine she felt she received no benefit from Mestinon. After a week the medication was discontinued, but despite resumption of neostigmine these unusual side reactions began to improve only after six weeks. When the patient was last examined, she was very tense and nervous. Though therapy with Mestinon was definitely a failure, it seems likely that many of her reactions were emotional in origin. Though many bizarre complaints were described, the patient at no time complained of the gastrointestinal symptoms commonly associated with neostigmine and related drugs.

*Case 3.*—A 39 year old housewife developed myasthenia gravis during her first pregnancy at age 26. Weakness was generalized but most severe in her face, speech, and swallowing. Maintenance therapy had consisted of an average of 270 mg. of neostigmine daily, in addition to ephedrine. This program gave the patient sufficient relief of symptoms so that she could continue mild activity, but frequent respiratory infections resulted in peri-

odic exacerbations of her myasthenia. In January 1954 the patient was instructed to discontinue neostigmine and substitute 60 mg. Mestinon tablets as needed. She has continued on this program to the present time, definitely preferring Mestinon to neostigmine. She states that five Mestinon tablets give her the same strength as 16 to 20 neostigmine tablets. She had previously noted that neostigmine took effect in 10 to 15 minutes and lasted about one hour. On the other hand, the effect of Mestinon lasts about four hours. She thought that Mestinon took about 30 minutes to take effect but was not sure, because she did not experience the quick let-down that she did when using neostigmine. The effect of each Mestinon tablet seemed to grade into the other. For these reasons she preferred Mestinon, though she did not seem to feel that it improved her total strength significantly better than neostigmine. She had noted no side effects from the maintenance dose of either neostigmine or Mestinon.

*Case 4.*—A 41 year old laborer first developed mild symptoms of myasthenia gravis at age 18. At the age of 33 his symptoms became more severe, the extraocular muscles and hands being most seriously affected. Maintenance therapy consisted of ephedrine, potassium, and an average of 180 mg. of neostigmine daily. In January 1954 he was instructed to discontinue neostigmine and begin Mestinon. He has continued Mestinon to the present time, definitely preferring it to neostigmine. On his required daily dose of neostigmine, abdominal cramps were a significant side reaction, necessitating the use of atropine. The patient had difficulty adjusting the dosage of atropine against the neostigmine sufficiently well to eliminate these cramps. On Mestinon he noted no side reactions. He required 300 to 420 mg. of Mestinon daily. The effect of both medications seemed to begin in about 30 minutes, but the effect of Mestinon lasted about four hours as compared with an hour and a half to two hours for neostigmine. He felt that Mestinon improved the strength in his arms more than neostigmine, and that it generally improved his strength and appetite. He noted that Mestinon's effect persisted better through the night and he wakened stronger in the morning. Clinical reexamination while on Mestinon disclosed no demonstrable significant difference than when the patient was taking neostigmine.

*Case 5.*—A 19 year old school girl first developed symptoms of myasthenia gravis associated with thyrotoxicosis in January 1953. The latter was successfully treated with radioactive iodine, but severe symptoms of myasthenia gravis remained, involving all muscle groups, the worst being the upper extremities and extraocular muscles. Thymectomy had been performed. Optimum maintenance therapy required an average of 600 mg. of neostigmine daily, ephedrine, potassium, and tetraethylpyrophosphate. In January 1954 the patient was instructed to discontinue neostigmine and begin Mestinon. No change was made in her other medications. She has continued Mestinon to the present time, taking from 720 to 1,080 mg. each day. She finds that the effect of Mestinon lasts about two hours as compared with one hour for neostigmine. Both medications take effect in about 30 minutes. Occasional abdominal cramps were noted with neostigmine. Mestinon produced no side effects at any time. Though her strength was improved about equally with both medications, the patient felt that she had less diplopia when taking Mestinon and stated she could read for longer periods of time. Clinical examination of the patient showed no significant objective change in strength in comparing the effect of the two medications.

*Case 6.*—A 17 year old school girl developed myasthenia gravis at the age of 16. Weakness was most pronounced in the arms and the bulbar musculature. Thymectomy had been performed. Maintenance therapy had consisted of an average of 360 mg. of neostigmine daily in addition to ephedrine and potassium. On this program she noted no significant side reactions. Her general strength was fairly good, but her voice was only slightly improved. In January 1954 she was instructed to substitute Mestinon for neostigmine. She has remained on Mestinon except for one week, during which she returned to neostigmine to verify her statements regarding comparisons between the two medicines. She found that 14 Mestinon tablets (840 mg.) equaled the effect of 24 tablets of neostigmine (360 mg.). Both medications took an hour to give effect. The action of neostigmine lasted about

two hours, as compared with four for Mestinon. No side effects were noted with either medication. The patient felt that though her general strength was about the same when taking either drug, her voice was significantly more improved on Mestinon. Though definite slurring was evident on repeated examinations, there was no doubt that her voice was better than at any other time during the year she was maintained on neostigmine. To determine whether or not her improvement was related to Mestinon therapy or thymectomy, she was advised to return to neostigmine for a two week period. After several days her voice again became much worse. When Mestinon was resumed and neostigmine discontinued, her voice again improved.

*Case 7.*—A 37 year old Negro laborer first developed myasthenia gravis in July 1953. The onset was rather sudden and severe, the extremities being much more involved than the cranial nerve muscles. Initial regulation of medication was difficult with dosages up to 1,050 mg. of neostigmine required daily, in addition to ephedrine and potassium. However, tetraethylpyrophosphate therapy was begun, and by December 1953 the patient seemed to be well stabilized on 300 mg. of neostigmine daily, in addition to the other medications. In January 1954 the patient was advised to substitute Mestinon for neostigmine, taking the supplementary medications without change. He found that a 60 mg. tablet taken three times daily gave him greater total strength than did the previous therapeutic dosage of neostigmine. His legs and jaws particularly felt stronger. He stated that Mestinon took an hour to take effect as compared with 45 minutes for neostigmine, but that the neostigmine effect lasted only about two hours, while Mestinon lasted four hours and its effect waned slowly. Cholinergic side reactions were present only at a time when the patient's neostigmine dosage was being correlated with phosphate therapy, and on a stabilized program there were no significant side effects with either medication.

To ascertain whether the improvement was perhaps coincidental with greater experience with the use of tetraethylpyrophosphate, the patient was withdrawn from Mestinon and returned to neostigmine for a week, but he found that he quickly returned to the same status as before and he felt that his condition was worse than when taking Mestinon.

*Case 8.*—A 48 year old housewife developed mild myasthenia gravis in 1948. Mild generalized weakness and diplopia were well controlled with 60 to 90 mg. of neostigmine daily without exacerbations. In March 1954 the patient was advised to substitute Mestinon for neostigmine. She finds that three 60 mg. Mestinon tablets are equivalent to her previous dosage of neostigmine. Both drugs act in about 15 minutes, but the Mestinon effect lasts for about four hours as compared with two or three hours of effect from each neostigmine tablet. The patient had noted occasional mild nausea from neostigmine, and though this symptom was not frequent enough to be very troublesome, she stated that Mestinon produced no side reactions. The patient thought that Mestinon might have improved her strength a little more than did neostigmine, but she felt that the difference was not great enough to be significant. However, when asked to resume neostigmine so that the Mestinon supply could be conserved, she phoned after three days stating that she became weaker when she returned to neostigmine therapy. She therefore felt she had made a mistake and that Mestinon definitely gave her greater strength.

*Case 9.*—A 37 year old Negro nurse had typical myasthenia gravis since 1948. Weakness was generalized. The patient had had several exacerbations with remissions, but she had been stabilized for the past two years and was doing well on seven or eight neostigmine tablets daily, in addition to ephedrine and potassium. On November 18, 1953 the patient was advised to substitute Mestinon for neostigmine, continuing the supplementary drugs unchanged. She has continued on this program to the present time. She found that two to three Mestinon tablets (120 to 180 mg.) gave her the same strength as her previous dosage of neostigmine. The effect of Mestinon lasts six or seven hours as compared with three or four hours for neostigmine, both medications taking effect within 15 to 30 minutes. This patient was in the habit of taking neostigmine sublingually, because she thought it was a simpler method of administration. However, since she took

so few Mestinon tablets, she did not bother to use the sublingual route except on one occasion. It was just as effective orally, and the tablet dissolved in three minutes. It left a mild chalky taste in her mouth, while neostigmine left no taste. The patient noted no great difference in her total strength while taking Mestinon. However, she did note that in the morning she did not have to take Mestinon before getting up as she had with neostigmine, and she could therefore rise promptly and begin her morning activities while waiting for her morning medication to take effect. For this reason she preferred Mestinon to neostigmine. Side effects were no problem on therapeutic dosages of either drug. While taking Mestinon she decided to return to work as a nurse for the first time since she developed myasthenia, and found no difficulty doing so. However, when her supply of Mestinon was gone and she returned to neostigmine therapy, she called requesting more Mestinon. She experienced great difficulty working while taking neostigmine, and had definitely decided that Mestinon was more effective in maintaining optimum and steady strength.

*Case 10.*—A 23 year old housewife began to tire easily in 1947 at the age of 17, and one year later had progression of symptoms with weakness of hip girdle, ptosis, diplopia, and bulbar paresis. The patient improved during her first pregnancy, but following an easy delivery in September 1950 she had severe exacerbation of the myasthenia with little improvement since then. Therapeutic abortion and sterilization were performed in June 1953 because of her poor condition. Mestinon was first given November 13, 1953. A month later she reported little change in her over-all strength. She was taking seven 60 mg. tablets of Mestinon in place of ten to 12 15 mg. tablets of neostigmine, together with tetraethylpyrophosphate and ephedrine. She immediately noted that she needed less atropine when taking Mestinon. She felt that Mestinon acted as quickly as neostigmine, that the duration of action was the same, but that it was not superior to neostigmine in the strength obtained.

She was then advised to stop tetraethylpyrophosphate and to take Mestinon as needed, continuing ephedrine as before. On return one month later she was taking 12 tablets of Mestinon and no atropine. Her appetite was improved and her strength somewhat better. She was doing more housework than previously. She stated that the effect of Mestinon lasted through the night much better than neostigmine and compared it in this respect to tetraethylpyrophosphate. Examination at this time showed improvement in the strength of her atrophic quadriceps for the first time since her postpartum relapse.

In March 1954 the patient returned, stating that she believed she had obtained a cumulative effect from her Mestinon and began to have a constant bearing down pain in the lower abdomen, with some cramping and diarrhea but no nausea or vomiting. The dosage was reduced to six to seven tablets of Mestinon daily and she took 0.4 mg. of atropine with each tablet of Mestinon. On this program she had neither a Mestinon reaction nor an atropine reaction. Because she was evidently experiencing a remission, she was asked to substitute neostigmine abruptly for Mestinon for one week to compare effectiveness. On two occasions she tried this, but found that with 12 to 14 tablets of neostigmine daily she became progressively weaker and resumed Mestinon after three days each time. She found that it took two days for the effect of Mestinon to disappear after it was stopped. Again she stated that while taking Mestinon she felt much the same all day and had better strength in the morning. Mestinon did not take effect as promptly as neostigmine, but she did not experience any let-down.

*Case 11.*—A 19 year old college student began to have symptoms of myasthenia gravis in 1951. She complained of trouble with chewing, swallowing, and speaking, as well as weakness in the extremities. The diagnosis of myasthenia gravis was first made in 1953 and the patient's course has been fluctuating since that time. Mestinon was first given on February 2, 1954, when the patient entered the hospital because of difficulty in swallowing. At that time she was taking 525 mg. of neostigmine daily, together with ephedrine, potassium, and atropine.

Six weeks later the patient reported that she was taking three tablets of Mestinon

(180 mg.) every four hours instead of four tablets of neostigmine (60 mg.) every two hours, with other medications unchanged. She stated that she was much better and preferred Mestinon to neostigmine because 1) she had had no cramps and required no atropine; 2) she had had no nausea and had gained weight as a result of better appetite and improvement in swallowing; 3) the Mestinon effect lasted longer; 4) she did not experience periodic let-down in strength during the day; 5) she was stronger than she had been on neostigmine.

On April 13 the patient reported that she was taking 15 or 16 tablets of Mestinon with no atropine and no side reactions. Dysarthria was her only complaint although she showed other involvement on examination. Again she said that her speech and general strength remained constant on Mestinon, and even on awakening in the morning she felt that she had maintained better strength with the new drug. She had tried substituting 18 tablets of neostigmine daily for Mestinon, but she resumed Mestinon again because she felt it gave her greater strength.

*Case 12.*—A 64 year old Negro male had onset in 1944 of myasthenia gravis which became progressively more severe in spite of treatment. Thymectomy was carried out the same year. Improvement occurred gradually following operation and for seven years the patient had been maintained on phosphate therapy, taking in addition about half a tablet of neostigmine two to three times each week. Mestinon was prescribed on December 28, 1953 in half-tablet dosage (30 mg.). On April 2 he reported that he had used Mestinon in amounts equivalent to his previous dosage of neostigmine and said he could not tell how long it took to act. He did state that neostigmine had always given him a disagreeable increased weakness about 10 minutes after its use and then his strength would begin to improve. He did not experience this with the gradual increase in strength from Mestinon. Initially he noted no difference in maximum strength or in duration of action. After trying alternating courses of neostigmine and Mestinon, this patient, who had been definitely prejudiced against the new drug before taking it, concluded that Mestinon was definitely superior in duration and gave him greater strength with a deeper feeling of security. In his alternating course he had used twice as many tablets of neostigmine as Mestinon.

*Case 13.*—A 50 year old mechanic began in April 1947 to have stiffness and weakness of his neck, followed shortly by difficulty with chewing, speaking, and swallowing. He then developed a shuffling gait. A diagnosis of myasthenia gravis was made, and the patient was found to have a mediastinal mass. At thoracotomy a thymic tumor which was locally infiltrating the pleura was removed. Myasthenic symptoms, always mild, continued to be controlled by one tablet of neostigmine three times daily until 1953, when the patient had exacerbation of symptoms and neostigmine was increased to eight tablets (120 mg.) a day, together with ephedrine and potassium. Mestinon was first given on March 17, 1954.

On April 17 he reported that he took one tablet of Mestinon for every two of neostigmine and felt that the new drug's effect lasted a little longer, although they both took effect within one hour. He had no ill effects from either drug. He said Mestinon made him stronger and he preferred it for this reason. Side reactions did not accompany therapeutic dosages of either medication.

*Case 14.*—A 37 year old housewife first developed myasthenia gravis in 1951. Weakness was generalized, perhaps more severe in the upper extremities. The patient had been stabilized on an average of 150 mg. of neostigmine daily, in addition to ephedrine. She obtained good results on this program except that for three or four days before each menstrual period it did not seem as effective as at other times. In March 1954 she was advised to substitute Mestinon for neostigmine and has continued this program to date. The patient used three or four tablets of atropine daily to control abdominal cramps when taking neostigmine, but with Mestinon there were no side reactions. She stated that she felt much "safer" when taking Mestinon. Four to seven 60 mg. Mestinon tablets equaled the effect of her previous dose of neostigmine and in fact made her feel stronger. She noted

that the let-down preceding her menstrual period did not occur with Mestinon. Both medications acted in about 15 minutes, but the Mestinon effect lasted three to four hours as compared with an average of two hours for neostigmine. The patient was particularly pleased that she could get up in the morning and begin activity rather than waiting in bed until her morning medication took effect. In all respects the patient preferred Mestinon.

*Case 15.*—A 23 year old housewife first developed myasthenia gravis in 1950 at the age of 19. Symptoms included weakness of the fingers initially, then diplopia, ptosis, dysphagia, dysarthria, and in 1953 severe weakness of the extremities. The diagnosis was made in 1951 and maintenance therapy with neostigmine and ephedrine was begun. She had always had difficulty controlling cramps and diarrhea and had tried various antispasmodics to overcome these side reactions of neostigmine. Because of increase in symptoms tetraethylpyrophosphate was added to the therapeutic program. Reactions to neostigmine and tetraethylpyrophosphate continued to be troublesome, and the patient was never able to maintain optimum dosage. She was taking four to five tablets (60 to 75 mg.) of neostigmine daily in addition to tetraethylpyrophosphate when Mestinon was first given in December 1953.

In January 1954 she reported that she had tried from two to seven tablets (120 to 420 mg.) of Mestinon daily, averaging about four or five. She was definite in her statement that it took two hours for Mestinon to become effective instead of the 30 minutes with neostigmine. The duration of both was said to be three hours. She believed the drugs afforded her equal strength, but she much preferred Mestinon because she had no severe reactions but only occasional diarrhea without pain, nausea, or vomiting.

*Case 16.*—A 46 year old housewife developed myasthenia at the age of 37. Her disorder was characterized primarily by ptosis, diplopia, and mild weakness of the extremities. Thyrotoxicosis occurring in 1951 was treated satisfactorily with radioactive iodine.

Mestinon was given January 22, 1954. In April the patient reported that she took six or seven tablets of Mestinon (360 to 420 mg.) each day in place of ten to 12 tablets (150 to 180 mg.) of neostigmine. She preferred Mestinon because she did not have any side reactions from it, whereas neostigmine produced cramps, anorexia, and some spasm of the esophagus. She said that she could not take neostigmine comfortably on an empty stomach but took Mestinon while shopping, before breakfast, and so on. She also stated that she could drive a car while taking Mestinon because her eyelids retracted longer and she felt that the strength gained in this respect was greater, although it was more probable that it was a prolongation of the drug's effect rather than any increase in maximum strength. She had to stop driving when she resumed neostigmine.

*Case 17.*—A 47 year old housewife first developed myasthenia gravis in 1942. She was first seen in 1954 because of a severe neostigmine reaction with pronounced muscular twitching, diaphoresis, weakness, cramps, and diarrhea. She was taking ten to 12 tablets (150 to 180 mg.) of neostigmine daily. The patient began taking Mestinon in March 1954. One month later she reported that she was taking six Mestinon tablets daily (360 mg.) and was delighted with the absence of reactions, noting only increased salivation and perspiring. She said that Mestinon did not make her as strong as neostigmine but the difference was not marked. She noted, however, that she did not have periods of increased weakness or let-down when taking Mestinon.

*Case 18.*—A 28 year old housewife developed myasthenia gravis in 1948. Symptoms have continued to be severe, with greatest difficulty in speaking, chewing, and swallowing. She was taking tetraethylpyrophosphate, ephedrine, atropine, and 150 mg. of neostigmine daily until January 7, 1954. At that time she was given Mestinon to substitute for neostigmine. The other medications were not changed. She kept a diary of her dosage and reactions, noting that the first dose of Mestinon did not increase strength much. When she repeated the dose twice at one hour intervals she began to note improvement. She varied her dose from five to 14 tablets and found that strength improved over the next

two or three days. Mestinon was withdrawn on January 20, 1954, and for one week the patient resumed neostigmine. During this week she increased neostigmine to 300 mg. daily and also increased the dosage of tetraethylpyrophosphate. In spite of this she said, "I was very weak during this – arms weak and unable to eat." When she resumed Mestinon her strength again improved over a two day period, but as she took larger amounts of Mestinon she began to have toxic symptoms not like her usual reaction to too much medication. Her symptoms consisted of constant abdominal aching and cramps, with frequent bowel movements but no nausea or vomiting.

In April she reported that, by decreasing tetraethylpyrophosphate while taking Mestinon, she had avoided any reactions and was taking ten tablets of Mestinon each day. Each time she resumed the use of neostigmine she became weaker in spite of concomitantly increasing the tetraethylpyrophosphate. She found that Mestinon made her stronger and its effect also lasted longer, particular overnight. She preferred to continue Mestinon therapy.

*Case 19.*—A 27 year old single woman had onset of ptosis, diplopia, dysarthria, and dysphagia in 1944, and experienced generalized weakness a few months later. Neostigmine was first given six months after onset, and the patient was also given radiation treatment with 200 roentgens to the upper mediastinum. She improved slowly over the next ten years. At the time Mestinon treatment was begun on March 22, 1954, the patient was taking 14 tablets of neostigmine (210 mg.) each day in addition to ephedrine. She did not require atropine, having no side effects from her medication.

She reported that she took eight Mestinon tablets (480 mg.) a day. She noticed little difference in the new medication except that it lasted longer (three to four hours compared to two hours for neostigmine). She thought that her ptosis and facial expression were a little better with Mestinon, but was not sure because of daily variability. She had tried doubling her dose of Mestinon, and found, as she had before with neostigmine, that it made no difference in her strength but produced "only a kind of burning feeling in my stomach and a little diarrhea."

*Case 20.*—A 46 year old die setter developed myasthenia gravis in 1952. He was maintained on tetraethylpyrophosphate plus 75 mg. of neostigmine per day. On January 5, 1954 the patient was given Mestinon to substitute for neostigmine, maintaining the tetraethylpyrophosphate at previous levels. The patient first reported that he found 300 mg. of Mestinon much more effective than neostigmine, that it gave longer lasting results per tablet, and was much less toxic. He noted that food did not dissipate the Mestinon effect as it did with neostigmine. He requested additional Mestinon and continued the atropine dosage unchanged.

On a later visit he reported that he was taking only two or three tablets of Mestinon (120 to 180 mg.) daily in addition to tetraethylpyrophosphate, although he had returned to work in the interim. He was well satisfied with his progress and preferred Mestinon, although he said that neostigmine gave him greater strength for a brief period.

*Case 21.*—A 43 year old automotive foreman developed myasthenia gravis in 1946. He had only minimal weakness in his extremities, but dysphagia and dysarthria were troublesome. Maintenance therapy consisted of tetraethylpyrophosphate and 45 mg. of neostigmine daily. Higher dosages caused troublesome side reactions.

A trial on Mestinon therapy was begun in March 1954. After one week the patient found that 180 mg. of Mestinon gave better strength than did neostigmine. More important, the side reactions of cramping abdominal pains were much less pronounced and he no longer found it necessary to use atropine. He began to decrease the tetraethylpyrophosphate dosage and increase Mestinon, stating that he felt just as well and side reactions were further reduced. He could not tell how long it took Mestinon to become effective after a given dose because it was too even in its action.

He then substituted neostigmine for Mestinon for one week, taking only three tablets (45 mg.) each day. He stated that he was afraid to take more because of "cramps," in

spite of taking six to eight atropine tablets daily. Apparently he gained greater strength from Mestinon because he could tolerate larger dosages.

*Case 22.*—A 40 year old school teacher has had myasthenia gravis for seven years. Symptoms are relatively mild but the patient has had very severe neostigmine reactions consisting of muscle twitching, vomiting, and prostration. She was taking six to 12 tablets (90 to 180 mg.) of neostigmine at the time Mestinon was first prescribed. After a month on Mestinon she reported that her strength was better in the morning and that it also carried her along more evenly during the day. Reactions to the medication were rare and mild and she no longer used atropine. She was taking three to five tablets per day (180 to 300 mg.).

## DISCUSSION

Twenty-two patients with myasthenia gravis were given Mestinon bromide. The age of the patients ranged from 17 to 64 years; there were 16 females and six males. The longest period of observation was seven months and the shortest, three months. Symptoms ranged from mild to severe in various patients. The maintenance dose of Mestinon ranged from 90 mg. to 900 mg. per day. Most patients found that 60 mg. of Mestinon was equivalent to 30 mg. of neostigmine, therefore using about half as many tablets of Mestinon.

Of the 22 patients given the drug, all but one (95 per cent) preferred it to neostigmine. Fifteen, or 68 per cent, stated that it gave them greater strength, and five, or 24 per cent, found it equal to neostigmine in the maximum strength it produced. Two patients, or 9 per cent, found that it gave them less strength than neostigmine. All patients found that the duration of effect of Mestinon was longer, but the important difference to most patients was the maintenance of strength on an even level without the necessity of frequent rest periods to regain strength, which they needed while taking neostigmine. Most patients also stated that they could scarcely tell when Mestinon began to exert its effect because of the gradual increase in strength it provided. Others stated that it took longer to act, and a few noted no difference.

While many patients reported greater strength on Mestinon than with neostigmine, it is felt that this was due to either of two factors: 1) the greater stability of strength with less fatiguability, or 2) their ability to take larger doses because of greater tolerance to the drug. In very few cases did Mestinon alleviate the major residual weakness, whether ocular, bulbar, or peripheral, which was present on neostigmine therapy. In other words the site of action was the same as was that of neostigmine.

Seibert[5] reported that Mestinon was most effective on the skeletal muscles, less favorable on bulbar muscles, and least effective on the extraocular muscles. Although in general this is true of both neostigmine and Mestinon, many myasthenics have greatest weakness in hip or shoulder girdle with relatively good relief of ocular and bulbar symptoms on either drug. In these patients the pattern of strength remained the same with Mestinon as it had been with neostigmine. That is, the most severely affected muscles responded proportionately less than did the musculature with milder weakness, and Mestinon therefore has no superiority over neostigmine in this respect.

One signal advantage of the new drug proved to be its decreased toxicity

and absence of muscarinic effects. Such side effects of Mestinon as occurred were mild and only in one case did the patient discontinue Mestinon because of any ill effect. In this patient none of the untoward reactions concerned the gastrointestinal tract but consisted of paresthesias, nervousness, and weakness which persisted for six weeks after one week's treatment with Mestinon.

One patient who experienced swelling of the lips from neostigmine had none of this apparently allergic reaction to Mestinon. Preference for Mestinon occurred in mild as well as severe myasthenics, but undoubtedly the greater benefit in maintaining strength was experienced by patients with severe symptoms. Patients frequently remarked on the persistence of effect overnight.

## CONCLUSIONS

1. Twenty-two patients with myasthenia gravis were given Mestinon bromide to replace neostigmine in their treatment.

2. Twenty-one, or 95 per cent, of the patients preferred Mestinon to neostigmine.

3. Mestinon gave more prolonged effect and more even maintenance of strength than did neostigmine.

4. Side effects or toxic reactions to Mestinon were minimal.

5. Mestinon was effective either given alone or in conjunction with ephedrine, potassium, or tetraethylpyrophosphate.

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# Migraine and Tension Headaches

## A Clinical Study of Two Thousand Cases

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ALTHOUGH headache occurs in a wide variety of clinical conditions and is treated by a host of therapeutic procedures, the basic mechanism of most headaches is stimulation of pain sensitive structures in and around blood vessels. Among this group are headaches associated with hypertension, arteriosclerosis, infection, brain tumor, hematoma, allergy, and cranial trauma. These conditions are responsible for the symptom in only a small percentage of the cases who consult a physician because of headache. In the vast majority of the cases the symptoms either are due to migraine or are primarily associated with an emotional disturbance (tension headache). It is our purpose to consider only these two types and to summarize our experiences with 2,000 patients suffering from migraine or tension headaches. These patients were studied and treated during the past seven years.

### PART 1 – MIGRAINE

#### CHARACTERISTICS

Although migraine probably may be due to many causes, it is a clear-cut clinical entity and the symptoms have a common underlying mechanism whatever the cause may be. It may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral, and throbbing. The headache occurs against a background of relative well-being, is often preceded by visual or psychologic disturbances, and is usually associated with vomiting and irritability. Frequently there is a history of similar headaches in the parents or other members of the family.

Analysis of one thousand patients with migraine revealed the following characteristics:

A history of migraine in the family occurred in 65 per cent. Seventy per cent were females or a ratio of more than two to one. The headaches begin as a rule before the age of 20 (55 per cent), onset after 40 being exceptional.

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The attacks occurred less than once weekly in 60 per cent of the patients. Daily headaches were very infrequent. The duration of the headache was less than one day in about one-half of the patients.

Prodromata were present in three out of four patients and were of considerable variability, including visual disorders, gastrointestinal irregularities, and disturbances of the psyche and of the autonomic nervous system.

The quality of the headache may be diverse but was most frequently throbbing (80 per cent). Migraine headaches were usually unilateral (80 per cent), with the majority occurring in the supraorbital frontal region (55 per cent).

Many contributing causes were alleged to initiate the attacks. Among these, emotional disturbances, fatigue, and menstruation seemed more frequent and acceptable, although alcohol, weather, and diet were also implicated.

During the headache phase a majority of the patients were usually quite ill. Among the more prominent complaints were nausea and vomiting, emotional disturbances, photophobia, and disturbances of the autonomic nervous system (pallor, sweating, flushing, and so on).

The diagnosis of migraine headache is essentially based on the clinical history and requires the presence of several of the following factors.[1]

1. Recurrent throbbing headaches, usually unilateral at onset, occurring against a background of relative well-being.
2. Nausea, vomiting, and irritability, occurring at the height of an attack.
3. Temporary visual disorders preceding the headache, including scintillating scotomata, photophobia, hemianopsia, and/or blurred vision.
4. History of migraine in the immediate family.
5. Symptoms such as paresthesias, speech disorders, dizziness, sweating, and other vasomotor disorders.
6. Relief by ergotamine.
7. Personality characteristics of inflexibility and shyness in childhood, giving rise to adult perfectionism, rigidity and resentment, ambitiousness and efficiency; a constitutional predisposition to sustained emotional states.

The clinical picture of migraine, as we have outlined it, indicates widespread bodily disturbance. Although attention is usually first called to the headache, there are numerous other symptoms to be considered as part of the entire picture.

### OBJECTIVE EVALUATION OF PATIENTS

There was no specificity as to body type. Neither general physical nor neurologic examinations were contributory. Routine laboratory studies such as blood counts, urinalysis, and skull roentgenograms were equally unrevealing. Ophthalmologic evaluation, including visual field studies, only rarely revealed any disorder. In our series no striking variation from the normal electroencephalogram was noted, although Dow and Whitty indicate that a large number of abnormal records without specific patterns occurred in their migraine patients.[2] Engel and his associates were able to demonstrate

electroencephalographic changes accompanying the prodromal visual scotomas.[3,4]

Water balance studies were performed on ten of our patients to determine whether there is any relation between fluid retention per se and the development of headache. The patients were hydrated with intravenous infusions after which an antidiuretic hormone and later a diuretic hormone were administered. No abnormal findings were obtained in any of these patients and none developed headache during or subsequent to the tests.

An attempt was made to ascertain whether or not there is any dysfunction in the adrenal pituitary axis. Eosinophil counts were performed on 30 patients with migraine using a Spiers Chamber for the determination. In none of the patients were we able to demonstrate a basal eosinopenia (less than 70 cells per cu. mm.) or a basal eosinophilia (more than 450 cells per cu. mm.) either before or during a headache.

The Eosinopenic Response Test was performed, using corticotropin as the stimulus in eight patients and epinephrine in another eight patients. In all patients the circulating eosinophils fell at least 50 per cent four hours after the stimulus.

On the basis of these tests therefore, we are not able to relate migraine to a dysfunction of the pituitary-adrenal system. However, the sensitivity and validity of these tests are yet to be substantiated.

### UNUSUAL TYPES OF MIGRAINE

An interesting feature of migraine is that the syndrome is not limited to the head but may manifest itself in widespread disorganization of bodily function. The central and autonomic nervous system, the gastrointestinal, genitourinary system, and others may be involved. Thus associated disturbances often accompany the headache.

In some cases, these associated symptoms may serve as substitutes for the headache. Probably the most common migraine equivalent is that of periodic abdominal pain associated with nausea and vomiting. This is commensurate with the fact that many patients with migraine relate that early in childhood they had frequent attacks of cyclic vomiting which were associated with irritability and restlessness. These episodes were followed later in life by periodic attacks of unilateral headache. "Abdominal migraine" must be considered when an individual with history of typical migraine headache suffers from periodic attacks of abdominal pain for which no other mechanism can be demonstrated.[5–7]

Occasionally the pain seems to exist in the precordium radiating down to the axilla and left arm – "precordial migraine," also known as "thoracic migraine." In these cases the electrocardiogram shows no abnormal features and no clinical evidence is present to account for the symptoms.[8]

Rarely the substitute for the characteristic headache may be pain limited to the upper or lower extremities or to the pelvis or genitalia.

In ophthalmic migraine, temporary visual disturbances, such as hemianopsia, amblyopia, and scotomata, are simliar to the prodroma of classic migraine. However, these visual disturbances mark the height of an attack instead of the preliminary period.[9,10]

Ophthalmoplegic migraine is the term used to describe certain cases in which recurrent unilateral headaches are associated with extraocular palsies. The cause is unknown although recurrent pressure on an extraocular nerve due to dilatation of arteries has been suggested as a possibility. In other cases it appears that an aneurysm pressing on the cranial nerves is responsible. The third cranial nerve is usually affected and the pupil is almost always dilated. After the headache has been present a number of hours the palsy appears on the painful side and may persist for several days or many weeks after the headache had disappeared.[11,12] We have observed five such cases. The diagnosis of ophthalmic and ophthalmoplegic migraine should not be entertained until a vascular malformation, aneurysm, or brainstem lesion has been excluded.

## MECHANISM

### *Physiologic considerations*

Well substantiated observations from various sources have demonstrated that in an attack of migraine the following physiologic changes occur.[13–16] An initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other pre-headache phenomena prior to the onset of the headache. This prodromal period is followed by dilatation and distention of cranial arteries, primarily in the distribution of the external carotid artery. Stimulation of pain sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilatation results in a rigid, pipe-like state of the vessels. The pain at this stage is a steady ache replacing the earlier throbbing, pulsating type. During or following this, there is contraction of the neck muscles and "muscle-contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the headache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter or "muscle-pain" is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although in migraine the immediate cause of pain is associated with dilation of cranial arteries, it is evident that dilatation of blood vessels alone is not sufficient to produce headache.[17,18] Other dynamic or chemical factors as yet not clearly delineated must contribute.

### *Psychologic factors*

The importance of psychologic factors in the migraine attack is great.[19] Personality studies have indicated that many patients with migraine are meticulous, neat in appearance, rigid in their thinking, and excessively aggressive toward their environment. It is often noted that in their earlier life they have had considerable insecurity with resulting tensions which are manifested in inflexibility, overconscientiousness, meticulousness, perfectionism and resentment.[20–22]

In a recent study it was observed that psychodynamic mechanisms play an important role, even in migraine of young children.[23,24] The types of neurotic symptoms observed in children were varied and dramatic. They included temper tantrums, phobias, frequent nightmares, hairpulling, enuresis, obvious anxiety, hyperactivity, lethargy, thumbsucking, nailbiting, and feeding difficulties.

In patients of all ages a variety of psychogenic factors have been related to the headache. Attempts have been made to define specific personality patterns. In our experience the personality make-up in these people is extremely variable and may be influenced by a variety of emotional factors. Most of these are unconscious and include hostility, identification with a family figure, a wish to remain in a position of dependency, or a desire to gain love, affection, or attention. The most frequent conflicts are apparently concerned with hostile impulses associated with feelings of guilt.

There is little evidence of specificity of the precipitating psychodynamic factors. Not all patients with migraine are compulsive, perfectionistic, or rigid. A recent objective psychologic evaluation of our patients confirms this point of view. Repressed hostility is an extremely common factor among many persons who do not have migraine but may have hypertension, ulcers, or just a small bank account. Nevertheless, an understanding of the underlying psychologic factors plays an important part in the management of migraine, for in the ability of the patient to handle emotional tension lies the most satisfactory means of preventing the attacks in the majority of cases.

### CAUSE

The underlying causes of migraine are unknown. Many theories have been advanced but the large variety of precipitating factors and diversity of symptoms make it most difficult to explain all cases of migraine on any single etiologic basis.

It has been maintained by many that migraine is the result of a disorder of the endocrine system.[25–27] The frequent association of migraine with puberty, menstruation, and menopause has been emphasized as indicating a gonadal etiology. There is not, however, any physiologic or biochemical data to support this hypothesis.

One theory is that stimulation of hypophyseal adrenal mechanisms occurs during periods of stress. It has been postulated that exposure to noxious stimuli, either physiologic or psychologic, of sufficient or prolonged intensity results in the inability of the body to adapt to stress, which in turn causes certain vasomotor changes in the cranial circulation producing cranial pain. The mechanism by which the nervous and hormonal systems function in producing these physiologic changes is not clearly understood. It is possible that both the neural and hormonal mechanism could affect the vasomotor system via the hypothalamus and the sympathetic nervous system. It has been suggested that the symptoms may be the result of dysfunction of the pituitary-adrenal system. Disturbances in salt and water metabolism have been noted in some

migraine patients, but the results of our studies on water metabolism and on activity of the pituitary-adrenal system, mentioned above, do not support this hypothesis.

Allergy has been invoked as the causative factor in migraine attacks. There is no doubt that headaches may occasionally be precipitated by allergens in certain susceptible individuals, but investigations of the last few years have indicated that the role of allergy in causation of migraine has been overestimated.[28,29] Observations of our own material and those of others indicate that allergens may be the offenders in a small number of patients, and in these it probably acts as a trigger mechanism rather than as the primary cause of the attack.[30] Claims that food sensitivity may induce headache must be closely analyzed before being accepted.

The relationship between histamine sensitivity and migraine has been stressed by several investigators.[31,32] They have stated that a headache could be induced in patients with migraine by the injection of smaller amounts of histamine than in normal control persons. However, we were able to produce a similar result with chronic posttraumatic headache which indicates the relationship of histamine sensitivity to migraine is not necessarily specific or relevant. Furthermore, the use of other vasodilators, such as nitroglycerine, amyl nitrite, and carbon dioxide, produces the same effect as histamine. In our experience antihistaminic medication is of no value in migraine and only occasionally helps headaches of the type described as "histamine cephalalgia."

The importance of psychologic factors in migraine has long been recognized.[33–35] Studies indicate that in a great majority of patients with migraine there is a "personality pattern," one of the features of which is an abnormally strong reaction to environmental stress. It is doubtful whether psychologic mechanisms alone can be responsible for the chain of physiologic events noted in the migraine attack without some basic underlying lability in the physiology of these patients.

Heredity has been emphasized by all observers to be an important factor in migraine.[36] About 65 per cent of our patients reported migraine present in members of the immediate family. However, there is no evidence in regard to the exact mode of this inheritance, nor is there any evidence as to what specific abnormality may be inherited. In some instances and perhaps to a certain degree in all cases, there may be an inherent functional instability of the autonomic or possibly other systems. There is also the possibility that migraine occurs on a familial basis and is related to environmental rather than hereditary factors.

That anoxia might be the cause of migraine was proposed over 50 years ago.[37] In a few cases the use of a vasodilator drug early in an attack may abort the episode. Although the ergotamine derivatives produce vasoconstriction, they have been shown to lead to an increase in cerebral blood flow in animals. However, this has not been demonstrated in man and it is more probable that anoxia may be one of the accessory factors in the migraine syndrome rather than a basic cause.

Other investigators have proposed such varied etiologic mechanisms as vitamin deficiencies; intoxication from colonic, duodenal, or hepatic disorders; various ocular malfunctions; and trauma to the head and neck. There is no evidence to support such hypotheses.

From available information we may postulate that patients with migraine react poorly to stress for two reasons. First, there is a hereditary factor; the mechanism through which this hereditary factor operates has not been clearly elucidated, but is possibly related to an imbalance of the autonomic nervous system. Secondly, they have an insecure personality pattern which interferes with their adjustment to their environment. This sets a pattern of function which the limited physiologic capacity of the individual is unable to handle, resulting in cranial vascular changes which produce the headache.

### THERAPY

Treatment of migraine is difficult because the basic causes are unknown, the mechanism only partially understood, and the symptoms severe and tenacious.

In the treatment of migraine a variety of methods have been used and analyzed including pharmacotherapy, psychotherapy, physiotherapy, and surgery. It has been our experience that a dual approach using pharmacotherapy and psychotherapy is the most successful method of treatment.[38]

Symptomatic treatment of migraine is most effective by use of oral or rectal ergotamine tartrate and caffeine (Cafergot). Rectal use of Cafergot has proved empirically to be most efficacious, especially when oral medication cannot be retained. It is likely that rectal medication has the advantage of being absorbed more directly into the systemic circulation, without having to penetrate the hepatic and gastric barriers. Hence it is postulated that its action is quicker with less side effects than by oral administration. This requires further investigation.

*Dosage*: For each attack the average initial oral dose of Cafergot (each tablet contains ergotamine tartrate 1 mg. and caffeine 100 mg.) is two tablets, followed by one tablet at half-hour intervals until the necessary effect is produced (up to a total of six tablets). However, the minimum effective dose must be determined individually for each patient. Thus, in some cases the initial dose may be one tablet, while in others four tablets may be necessary at the first sign of a headache. Further, the severity of attacks varies from time to time in each patient and also from patient to patient, hence requiring some adjustment of dosage for each headache. The average rectal dose is one suppository (ergotamine tartrate 2 mg. and caffeine 100 mg.) every half hour, using a total of three suppositories if necessary.

The maximum dose of ergotamine per se is 10 mg. in any one day, and this maximum dose (ten tablets or five suppositories) should not be given more than once weekly. Not more than 0.5 mg. subcutaneously or 0.25 mg. intravenously of ergotamine tartrate should be administered in any single week.

The importance of administering the medication early in the course of an attack, as well as in adequate doses, cannot be overestimated. Many failures in therapy are caused by an inadequate dose given too late. The optimal time of administration is in the prodromal period or immediately after onset of the headache.

The side effects of ergotamine tartrate are variable and may include nausea, vomiting, tingling of hands and feet, pains in the neck, thigh, and abdomen, and substernal oppression.[39] In some cases, a careful history reveals that these symptoms are associated with the migraine proper and are not due to the medication. Muscle spasm of the extremities may occur and can be ameliorated by massage or exercise. Perivascular pain may also occur. Nausea and vomiting and intestinal spasm may be relieved by using atropine sulphate 0.65 mg. (1/100 gr.) before or during the administration of the medication.

In general, none of these symptoms, if transient, contraindicate the use of ergotamine tartrate in the absence of infection, or organic heart, hepatic, or peripheral vascular disease. If the patient develops persistent paresthesias, substernal oppression, or pain in the abdomen or extremities, the drug should be discontinued. Ergotamine is contraindicated in organic heart disease, obliterative vascular disease, hypertension, pregnancy, hepatic disease, and septic states associated with intravascular foci.

*D.H.E. therapy*: In some patients ergotamine tartrate is poorly tolerated and the use of dihydroergotamine methanesulfonate (D.H.E.-45) is indicated. Dihydrogenation of ergot reduces the vasoconstrictive action. In order to produce an equivalent therapeutic effect dihydroergotamine must be given in doses twice as great as ergotamine tartrate. It can only be administered parenterally and, like ergotamine, must be given as early as possible in the attack. The usual dose is 1 mg. intravenously or subcutaneously, to be repeated in an hour if necessary. The administration of dihydroergotamine is contraindicated in the presence of peripheral vascular disease, angina pectoris, impaired hepatic or renal function, septic states associated with intravascular foci, and in pregnancy.

Vasodilators such as histamine, B-methylacetylcholine (Mecholyl), nicotinic acid, amyl nitrite, intravenous magnesium sulphate, and so on have been used in the prodromal stage (vasoconstrictor phase) in order to abort the attack, and in the headache stage (vasodilator phase) to lower the blood pressure sufficiently to reduce the arterial pulsations. Except in a few isolated cases, these preparations are of little value.

Analgesics and sedatives are sometimes indicated if the headache has been present long enough for edema to take place and the vessels to become firm and tortuous. In these cases codeine phosphate (60 mg.) with or without sodium Amytal (0.2 gm.) or Seconal (0.1 gm.) is indicated.

We have so far evaluated over 50 different substances and combinations without significant success in any excepting those already mentioned.

PSYCHOTHERAPY

It is well known that suitable psychotherapy may be of great value in reducing the intensity and number of migraine attacks in most patients and may even result in their disappearance for a considerable time. As the type and principles of such therapy is the same for migraine and tension headache, this subject will be elaborated under therapy of tension headache.

FAILURES IN THERAPY

Even if one adheres closely to the principles just outlined, there remain about 15 per cent of patients who are refractory to symptomatic treatment and at least 35 per cent who are refractory to preventive methods.[40] It appears that the most significant factors in the refractory patients are as follows: 1) The family history in these cases reveals a preponderance of migraine in a ratio of 90 per cent in the refractory to 60 per cent in the non-refractory group. Whether this reflects a genetic or environmental factor is still open to question. 2) These patients apparently have a much lower headache threshold as represented by an intolerance to emotional trauma. It requires much less stress to precipitate an attack. This may represent an unstable autonomic system reaction to emotional stimuli. 3) The personality disturbances seem greater in degree although no specific personality type is manifest. In the refractory cases there appear to be more neurotic traits in childhood. As adults there is great rigidity, agression, and an inadequate sexual adjustment.

However, the most significant difference between the two groups is that in the refractory cases there is a pronounced deficiency in the mechanisms whereby patients handle their aggression.

MIGRAINE IN CHILDREN

Migraine is common in children but is diagnosed infrequently. There are several explanations for this incongruity. Subjective signs such as headache are often difficult to elicit in young children. The headache tends to be less severe and to recur less frequently than in adults.

Our conclusions based on a study of 100 children with migraine observed during the past six years at the Montefiore Hospital Headache Clinic and in private practice is that they do not differ from adults except that the headache may be overshadowed by abdominal complaints.[41]

## PART 2 – TENSION HEADACHE

CHARACTERISTICS

Tension headache is that type of headache occurring in relation to constant or periodic emotional conflicts concerning which patients are partially aware. Tension headaches have no prodroma, are usually bilateral, occipital, or frontal, and may be accompanied by a variety of associated signs, including anxiety, nausea, and vomiting. Frequency and duration are variable.

Reviewing the history of one thousand patients with tension headache it was noted that the majority are females (65 per cent).

A family history of headache was present in 40 per cent of the patients. The age of onset of headache in these patients would indicate that the majority began having headaches in the earlier decades (55 per cent between 20 and 40 years of age). Most of the tension headaches are gradual in onset and offset. With regard to frequency, 20 per cent claimed almost constant headache, with periodic exacerbations of greater severity. These patients stated that they were never really free from cranial discomfort. Daily headaches composed the largest group (30 per cent). Patients having headaches less often than once a week constituted only 15 per cent of our group. The severity and frequency of the headache served as a selective factor in our series because patients with mild or infrequent headaches do not usually seek specialized treatment.

The duration of the headache is extremely variable not only from case to case but also in the same individual. However, one out of five patients has constant headaches. In approximately one-third of the patients the headache lasts for many hours (one to 12) but it is rare for a patient to have a headache of less than one hour duration.

As a contributing factor there would appear to be a predominance of admitted emotional factors. It is our impression that emotional factors are present in 100 per cent of these cases.

Prodromata are usually not present (10 per cent). This lack of pre-headache phenomena is quite striking. Tension headaches are predominantly bilateral. Only 10 per cent of the patients complained of unilateral headaches. The majority of the patients describe their pain as "dull," "throbbing," or "pressure." However, the type of pain varies widely not only from patient to patient but also from time to time in the same patient. Associated symptoms were common accompaniments of the tension headaches. Those most frequently noted were anxiety and depression, nausea, and photophobia.

### COMPARISON OF MIGRAINE AND TENSION HEADACHE

In comparing migraine and tension headache certain clinical features appear to be characteristic of each, although there are wide variations in each group and the same individual may have both types of headaches (figure 1).

### MECHANISM

The mechanism by which cranial structures give rise to headache in patients with psychic distress may operate at two levels, each applicable to a different group of psychogenic headaches.

In one group (tension headache) the mental conflict may stimulate the sympathetic or autonomic nervous system with change in the calibre of blood vessels or stimulation of the somatic motor system with contraction of skeletal muscles, particularly those of the neck.

In another group (conversion headache) the symptom represents a specific unconscious symbolic meaning and conversion mechanisms are prevalent. This type of headache cannot be distinguished from tension headache

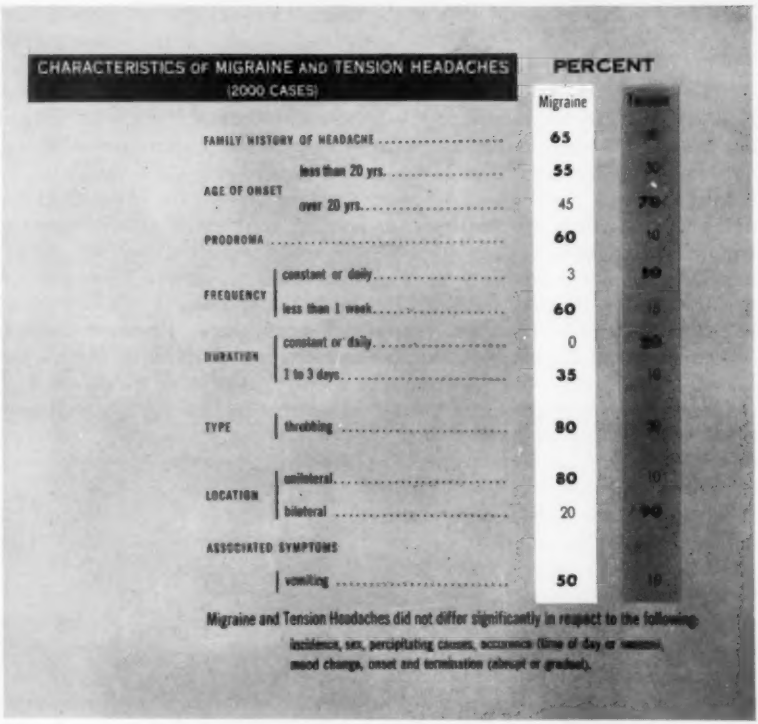


FIG. 1. Characteristics of migraine and tension headaches in 2,000 cases.

on the basis of its clinical description alone.

In tension headaches muscular or vascular mechanisms may act independently or concomitantly. With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysthesia in the neck and scalp. Associated with these muscular spasms may be ischemia which could be a contributory or primary factor in the induction of pain. It has also been hypothecated that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

Under stress a discharge may occur in the autonomic nervous system with resultant changes in the cranial blood vessels. The end organs for pain surrounding these blood vessels are stimulated and create nerve impulses which

pass along the afferent pathways to the central nervous system.

CAUSE

The actual cause of tension headache is unknown. However, there is good evidence that they are related to psychologic disturbances.[42] In a majority of our cases the fundamental psychic factors were largely unconscious, although most patients were aware of their anxiety. Environmental demands of an economic, social, physical, or intellectual nature beyond the capacity of the patient's personality may also produce somatic response of which headache is the major symptom. As in migraine the most frequently observed conflict in cases of tension headache were those over hostile impulses. These patients demonstrated aggression, hostility, and intense resentment against members of their family or persons who represent family figures. However, there is little evidence of specificity of the precipitating psychodynamic factors and as noted in migraine they may include identification, wish to remain in a position of dependence, means of gaining attention, and so on. Although these findings help us to understand the mechanism of certain headaches, they do not elucidate the cause. Why the same psychogenic factors previously discussed as initiating headaches through physiologic mechanisms may also produce them on a purely psychologic level, such as in conversion mechanisms, is unknown. Furthermore, the same type of psychologic conflict may produce a variety of symptoms, such as headache, ulcers, and hypertension, or may be present in an individual who is symptom-free.

Our present knowledge indicates that in tension headache, emotional conflicts which the patient has suppressed or repressed because of their unpleasant nature may produce a discharge, either skeletal or autonomic, with resultant changes in the muscles and blood vessels of the head and neck eventually productive of pain. The end organs for pain near these muscular and vascular changes are stimulated and create nerve impulses that pass along the afferent system to the central nervous system, where they are translated as painful sensations.

Muscular headaches differ from tension headaches in that the former occur with local muscle or nerve root injury, and secondarily, from noxious stimulation elsewhere in the head. The clinical features of the conditions causing the muscle spasm, for example, cervical disk, osteoarthritis, cord tumor, ocular inflammation, and so on, usually serve to differentiate these types of muscular headache from spasm associated with emotional tension.

TREATMENT

In the treatment of tension headaches we are obviously dealing with both physical and emotional factors. Therefore the goals of therapy are limited to the potentialities of the patient in therapy, the pharmacologic actions of the medications used, and the physician's interest and orientation toward the problem. The treatment of choice in tension headache is a combination of psychotherapy and drug therapy.

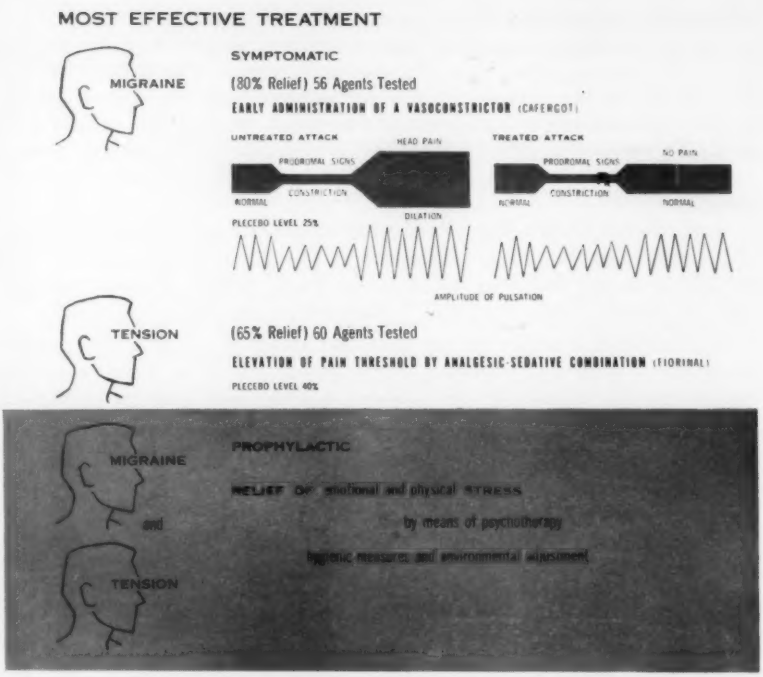


FIG. 2. Summary of treatment for migraine and tension headaches.

Psychotherapy is directed toward relieving the emotional tension and stress which is the precipitating factor in the attack of tension headache. The most important single factor in the psychotherapeutic process is the emotional relationship of the patient to the physician.[43] This relationship dominates the treatment, despite the fact that it may be explicitly discussed only rarely or not at all. In complete psychoanalysis, of course, this relationship is clearly recognized by the therapist.

In emphasizing the importance of the physician-patient relationship, one must not, of course, overlook the importance of other aspects of psychotherapeutic procedures as, for example, environmental manipulation and the ventilation of wholly or partly unconscious emotional conflicts by the patient.

In environmental management one has to recognize and deal with the patient's capacity to handle his work, recreation, family, and social life. The physician should strive to correct the patient's program so that work, play, and rest are balanced. In some cases a sustained hobby is of value in securing relief from tension and daily stress. Concerning any changes in the patient's way of life, it is important that the doctor assist the patient in making his own

decisions rather than that the physician make such decisions for him.

Often it is more practical and more satisfactory to have the patient adjust to his environment rather than alter the environment. This is done by ventilation, having the patient talk out his problem with the aim of gaining greater understanding of his emotional difficulties. He may thus achieve freedom from needless anxiety, enabling him in turn to cope with actual stressful situations. The physician must learn to listen patiently and create trust and confidence.

Often simple explanations of the effect emotions have on bodily functions and the relationship of stress situations to development of symptoms may give the patient insight into what occurs to him during periods of stress. Reassurance, suggestion, and re-education are other technics which may help.

Such therapy is within the province and ability of the interested general practitioner. With this treatment over-all improvement in terms of greater capacity for life adjustment and a reduction of the habit patterns which lead to activation of the physiologic mechanism causing the headache can be anticipated. In some patients where reorganization of the personality is necessary to secure relief, formalized psychiatric treatment is necessary.

Symptomatic relief from tension headache is secured by drug therapy, which as in psychotherapy, must have flexibility for its keynote. The treatment of tension headache is non-specific, but the purpose of therapy is to relieve tension and raise the pain threshold. This is best accomplished by use of an analgesic-sedative combination. Such a combination should react with the minimal side effects allowing the patient to maintain his environmental relations and not be a problem because of addiction potential or development of tolerance.

The efficiency of any drug does not depend on its pharmacologic action alone. The importance of dosage, timing, and mode of administration cannot be stressed sufficiently. Furthermore, its efficacy greatly depends upon the physician who is prescribing the medication and upon the length and frequency of his interviews with the patients. What the taking of medication symbolizes to the patient is also a contributory factor in treatment. Is the taking of medication a sign to the patients of weakness, of receiving omnipotent or mystical power, of love, and so on? These factors are rarely given consideration in evaluating therapeutic results.

In previous communications we have analyzed the results of our experiences in the treatment of tension headache.[44] Fifty different combinations of drugs were used in these studies. The most effective symptomatic medication in the treatment of tension headache have been several analgesic and sedative combinations. One of the most effective is Fiorinal, (isobutyl-allyl-barbituric acid 50 mg., caffeine 40 mg., acetylsalicylic acid 200 mg., and acetophenetidin 130 mg.) which yielded relief in two out of three patients (figure 2). Daprisal (d-Amphetamine sulfate 5.0 mg., amobarbital 32 mg., acetylsalicylic acid 162 mg., and acetophenetidin 162 mg.) was particularly effective in patients

when a depressive element was prominent. Approximately one out of two patients received some relief from placebos. This has been considered in our evaluation of therapy.

SUMMARY

Two thousand patients suffering from migraine and tension headache were studied during the past seven years. Migraine represents a definite clinical entity and may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral, and throbbing. It is preceded by an aura and is usually associated with vomiting. There is frequently a positive family history. It is our impression that the treatment of migraine is a complex, individualized procedure. Symptomatic treatment is essentially one of pharmacotherapy, and the best results have been obtained with the use of ergotamine derivatives, notably a compound of ergotamine and caffeine (Cafergot). Prevention of an attack is best accomplished by psychotherapy.

Tension headache is that type of headache occurring in relation to constant or periodic emotional conflicts. Tension headaches are usually bilateral and may be accompanied by a variety of associated signs, including anxiety, nausea, and vomiting. Frequency and duration are variable. The best symptomatic relief is obtained with analgesics and sedatives. The best prophylactic results are obtained by psychotherapy.

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# Failure of Muscular Dystrophy Treatment with a Protein Hydrolysate

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*and C. J. Pelletier, M.D.*

TREATMENT OF THE DYSTROPHIES remains unsatisfactory and inconclusive. A recent review of the subject[1] lists 82 substances and procedures which have been used in the treatment of the dystrophic syndromes. Some 34 of these substances and procedures have been reported as being of some therapeutic value at one time or another. The present report deals with yet another therapeutic regime which has previously resulted in objective and subjective improvement in a small group of muscular dystrophy patients.[2]

In view of this encouraging preliminary report on the therapeutic use of a protein hydrolysate together with large doses of folic acid and vitamin $B_{12}$, it was felt desirable to treat a larger series of cases by this procedure. The protein hydrolysate is prepared by the tryptic digest of milk casein. Each ounce of this product contains:

*Amino acids* – Alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, hydroxiproline, isoleucine, leucine, lycine, methionine, phenylalanine, proline, serine, threonine, trytophane, tyrosine, valine, and their peptides, as contained in approximately 16 gm. of protein hydrolysate (enzymatic digest of casein).

| | | |
|---|---|---|
| *Vitamins* – | Vitamin A | 5,000 U.S.P. units |
| | Vitamin D | 500 U.S.P. units |
| | Thiamine HCl | 10 mg. |
| | Riboflavin | 6 mg. |
| | Pyridoxine HCl | 1 mg. |
| | Calcium pantothenate | 1 mg. |
| | Niacinamide | 50 mg. |
| | Ascorbic acid | 100 mg. |
| *Minerals* – | Iron peptonate | 0.1 gm. |
| | Tribasic calcium phosphate | 1.0 gm. |

In addition to the protein hydrolysate, one capsule of Rubrafolin was given twice a day.

From the department of neurology, University Hospital, Ann Arbor, Michigan, and The Helene Meinke Hospital (Dr. Pelletier), Hazel Park, Michigan.

Read by title at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 29-May 1, 1954.

The treatment substances were given on the assumption that the wasting process in muscle which occurs in muscular dystrophy is secondary either to failure of the digestive system to split the protein molecule into the basic amino acids or to a disorder of the enzymatic system for the synthesis of muscle tissue. Van Meter[2] reported that definite and progressive improvement, objective and subjective, occurred in all ten cases of the previous series. At the time of his report the period of treatment had been from two months to one year, although only two patients had been treated for more than four months.

In the present series 42 patients with progressive muscular dystrophy were given one heaping teaspoonful of the protein hydrolysate three times a day, together with one capsule of Rubrafolin twice a day. Twenty-one of these patients were treated at the neurology clinic of the University Hospital, and 19 patients were followed in the Detroit area. The two groups are being reported together since the results are identical. However, it is important that during the investigation itself the two groups were treated and followed entirely independently. The observations herein reported represent the results of two independently controlled experiments. The same observational procedure was carried out in both groups.

All cases were evaluated clinically prior to treatment and again at the end of five months. Many patients were seen at monthly intervals and some have been followed for a period of six or seven months. None of the patients included in this series received any other form of therapy during the observation period, with the exception of those patients who continued on previously instituted programs of physical therapy. All patients or parents were instructed to keep written records of any objective or subjective alterations which occurred during the therapeutic trial.

In addition to 42 cases of muscular dystrophy, six cases of Charcot-Marie-Tooth disease, two cases of amyotrophic lateral sclerosis, and one case of amyotonia congenita were placed on the same therapeutic program. There were no cases of the facioscapulohumeral form of dystrophy in this series; all cases reported had the pseudohypertrophic form of muscular dystrophy.

Thirty patients of the series were confined in part or entirely to wheelchairs. The remaining 12 were still ambulatory in varying degrees.

There were 31 males and 11 females in the series, including five pairs of male siblings. A sixth sibship consisted of four males and one female. The average age of the group was 23, with a range from five to 57 years. The age distribution is as follows:

| *Age* | *Cases* | *Age* | *Cases* |
|---|---|---|---|
| 5-10 | 10 | 31-40 | 4 |
| 11-20 | 14 | 41-50 | 2 |
| 21-30 | 6 | 51-57 | 5 |

Duration of symptoms at the beginning treatment ranged from one to 43 years, with an average duration of 17 years. The distribution of duration of symptoms is as follows:

| Years | Cases | Years | Cases |
|---|---|---|---|
| 0-5 | 4 | 24-30 | 2 |
| 6-10 | 10 | 31-35 | 1 |
| 11-15 | 10 | 36-40 | 4 |
| 16-20 | 4 | 41-45 | 2 |
| 21-25 | 5 | | |

RESULTS OF TREATMENT

Despite the fact that a variety of biochemical changes are reported in muscular dystrophy, at the present time there is no biochemical procedure by which the results of therapy in muscular dystrophy can be accurately gauged. For this reason the results of treatment in this study are based entirely upon clinical evaluation.

At the time of this report none of the treated patients can be said to have had any objective improvement, although one patient states he has more strength in his upper extremities. This improvement cannot be verified objectively. Muscle strength, reflex examination, and muscle bulk were not measurably improved. Ability to walk or to rise from a sitting or supine position were not demonstrably improved in those cases not confined to a wheelchair.

Subjective reactions similar to those reported by Van Meter were experienced by several of the patients. The occurrence of muscle cramps was rare, but most of the patients reported a sense of generalized warmth shortly after beginning treatment. Many of the patients developed a feeling of well being and were considered by family and friends to be more cheerful and alert. Two of the children in the series were reported by their teachers to have shown some improvement in both attitude and studies.

The feeling of well being was not limited to the dystrophy group, but was noted in two cases of Charcot-Marie-Tooth neuromuscular atrophy and in both cases of amyotrophic lateral sclerosis. One of the latter, a patient with marked bulbar symptoms, wrote, "I feel wonderful, but I can't talk or swallow any better." Three of the dystrophy cases noted a feeling of well being and lessened fatigue during the first month, but felt that this improvement disappeared despite continued treatment.

It has been noted that in treating muscular dystrophy patients "clinical improvement is sought with anxious eye, with the result that some patients react favorably with subjective improvement each time a new substance is tried. This subjective improvement usually persists for periods of from two to five weeks but gradually subsides on continued administration." [1]

In the present series of cases, the reported subjective improvement is in part attributable to psychologic factors and in part probably the result of improved dietary intake. It is conceivable that many of these patients had received an inadequate diet deficient in protein. Thus, it may well be that many of the patients who are receiving amino acids, folic acid, and vitamins report that they feel much better as a result of improved nutrition. They experience less upper respiratory infection, and in many cases relatives report

a more pleasing disposition. However, patients did not show any increase in muscle strength, loosening of contractures, or other improvement of the myopathy itself.

Two of the patients reported but could not demonstrate an increase of muscular activity, in that they were able to lift their arms and reach better. Both were excessively overweight and lost considerable weight on the treatment. While this was hopeful at first, it was soon observed that they were not stronger because of increased muscular strength but because the strength that was there was being called upon to lift a lesser weight.

## SUMMARY AND CONCLUSIONS

A group of 42 patients with muscular dystrophy were treated with a protein hydrolysate, mineral, and vitamin supplemented diet for a period of four to six months.

In no case was there any objective clinical evidence of improvement of the dystrophic process. Subjective improvement was reported in resistance to infection, sense of well being, and affective tone, and in a few instances improvement in family and school relationships was reported.

The present study fails to confirm the previously reported therapeutic efficacy of protein hydrolysate and vitamin dietary supplements in the treatment of pseudohypertrophic muscular dystrophy.

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The materials used in this study were generously provided by Walker Laboratories of Mount Vernon, New York, E. R. Squibb and Sons, and the Muscular Dystrophy Associations of America, Inc., Ann Arbor chapter.

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# CLINICAL PATHOLOGIC CONFERENCE

*Raymond D. Adams, M.D.*

*Section Editor — with the assistance of E. P. Richardson, Jr., M.D.*

*Presented by Philip R. Dodge, M.D. and Bertram E. Sprofkin, M.D.*

PRESENTATION OF CASE

A 38 YEAR OLD HOUSEWIFE was admitted to the United States Army Hospital, Fort Campbell, Kentucky on November 24, 1953, because of pain in the neck of four years' duration and increasing difficulty in using the arms and legs for about one year.

The illness began insidiously with stiffness of the neck and right suboccipital pain during the first trimester of her fourth pregnancy. The pain continued intermittently throughout the pregnancy and appeared to lessen following a normal labor and delivery. Subsequently, the pain increased in intensity during menstrual periods. The patient complained of a deep pain which at times radiated upward and anteriorly from the point of origin in the right suboccipital region. Occasionally the pain was aggravated by coughing, sneezing, or yawning.

About a year before admission the patient noted clumsiness of her right hand and ataxia of gait. She became unable to recognize objects in her right hand and frequently dropped things when not watching what she was doing. Some actual weakness of the right hand was noted; at that time the left hand was affected minimally. Over the next few months the symptoms increased in severity. In February 1953 she was admitted to the neurosurgical service of Vanderbilt University Hospital. Examination at that time revealed weakness of grip and of the wrist extensors on the right. There was diminished pain and touch sensation over the flexor surface of the right fifth finger. Clonus was present at both ankles but was more sustained on the right. Two lumbar punctures were done; the cerebrospinal fluid protein was 64 mg. per cent on the first and 75 mg. per cent on the second examination. There were no other abnormalities.

Radiographs of the skull and cervical spine were interpreted as normal. A satisfactory cervical myelogram was considered negative. The dye was allowed to flow to the level of the foramen magnum. During myelography the patient complained of a marked increase in neck pain, and following this procedure the disability was greater. Walking became almost impossible and for the first time she developed urinary retention and obstipation. Weakness and sensory loss in the hands increased and the patient stated that her "hands felt like gravel." Although prior to myelography the right hand was involved more severely, the left hand became the less useful after this procedure. She was unable to use either hand in the dark. It became difficult for her to distinguish hot and cold with the hands, especially the right one. In addition to sensory loss she developed intense burning pain in the arms and hands, so that even the touch of bed clothes was extremely uncomfortable. At times she complained of an aching pain in the right leg.

During the spring and summer of 1953 there was gradual improvement. She became ambulatory and regained voluntary, though imperfect, control of bladder and bowel. The burning pain remitted, though paresthesias of the hands persisted. There was

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intense stiffness of the legs, and clonus occurred frequently.

In August 1953, the patient was examined at Strong Memorial Hospital, Rochester, New York. On that occasion no abnormalities of the cranial nerves were noted. Neck movements were free, although there was occipital pain on extreme anterior flexion of the neck. Amyotrophy of the right supraspinatus and interossei muscles was questioned. There was a spastic weakness of the legs; the left leg was the weaker. There was ataxia of arms and legs demonstrated on finger-to-nose and heel-to-shin testing; this was more pronounced when the eyes were shut, and again the left side was more involved. The deep tendon reflexes were increased in both arms and legs, the abdominal reflexes were absent, and bilateral Hoffmann and Babinski signs were elicited.

Position sense was absent in the fingers of both hands and vibratory sense was absent bilaterally. She was unaware of the presence of a coin placed in the palm of either hand. Position sense in the toes was intact; vibratory sense was unimpaired in the feet. Pain and temperature sensations were diminished over the right upper thigh, right side of the trunk to the level of the clavicle anteriorly and to shoulder tip posteriorly, and over the entire right arm. There was no consistent loss of tactile sensation.

On lumbar puncture there was an initial pressure of 90 mm. of cerebrospinal fluid. This fluid was clear, colorless, and contained no cells. The total protein was 90 mg. per cent. Bilateral compression of the jugular veins caused the pressure to rise slowly to 100 mm.; the level fell rapidly to 90 mm. on release of pressure. During this maneuver there was a marked increase in the suboccipital pain.

Radiographs of the skull and upper cervical spine were repeated and reported as negative.

During the following three months the subjective symptoms did not change significantly. In November 1953 the patient was admitted to the Army Hospital at Fort Campbell.

On examination there was some limitation of flexion and rotation of the cervical spine toward the right. This maneuver elicited pain in the neck and suboccipital region. No abnormalities of the cranial nerves were detected. Although all muscles were thin, there was no definite focal atrophy. There was severe, diffuse weakness of both arms with minimal spasticity, worse on the left. The gait was stiff and ataxic due to weakness and spasticity of both legs. A terminal tremor was evident on finger-to-nose and heel-to-shin testing; this was greater on the left side and seemed not to be accounted for entirely by the sensorimotor defect. All deep reflexes were exaggerated. The superficial abdominal reflexes were absent. There were bilateral Hoffmann and Babinski signs. On sensory examination there was loss of position sense in all fingers except the thumb of the right hand. There was no impairment of position sense in the left hand and only slight difficulty in appreciation of minor movements of the great toes. Vibratory sense was absent over the middle, ring, and little finger of the right hand and over the clavicles, rib cage, and iliac crests bilaterally. It was impossible for the patient to recognize objects placed in either hand. Discrimination of two points was reduced to greater than 4 cm. over the hands, fingers, and soles of the feet. There was hypalgesia of the right hand and arm which extended onto the trunk and over the upper part of the left arm. On the left the hypalgesia extended upward to the angle of the jaw anteriorly and over the posterior third of the head. The diminished pain sense involved the entire trunk on the right side and extended downward to the mid-abdomen on the left. There was slight hypalgesia over the lateral surface of the right leg. The changes were more consistent over the anterior surface of the trunk and there were minimal, if any, changes over the sacral dermatomes. The patient had slight difficulty in distinguishing hot from cold test tubes over approximately the same distribution as the hypalgesia. There was a slight defect in tactile sensation (cotton wool) over the palmar surface of the fingers bilaterally and considerable loss over the anterior and posterior aspects of the neck and posterior third of the scalp on the left side (figure 1). On November 25, 1953, an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. SPROFKIN: In summary, this 38 year old woman suffered from intermittent pain in the neck and right suboccipital regions for three years, but there were no associated sensorimotor symptoms until one year ago when, notwithstanding some fluctuation in her symptomatology, there was a steady progres-

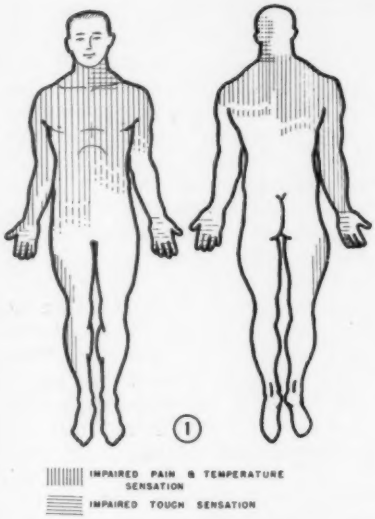


FIG. 1. Broken lines indicate a fading border of sensory loss. The severity of sensory loss varies indirectly with the width between lines.

sion of neurologic symptoms and signs. Within a few months after the onset of difficulty of gait and right manual clumsiness, a spastic quadriparesis, and a patchy dissociated type of sensory loss was demonstrable. Along with the transient exacerbation of symptoms following myelography, there developed sphincter disturbances and burning dysesthesias of both upper extremities. No focal atrophy was detected during the most recent examination. It was suggested that the tremor seemed out of proportion to the sensorimotor deficits, and again the patchy and dissociated nature of the sensory loss was emphasized. The hypalgesia extended to the borders of the trigeminal sensory fields but they were not involved. It was also reported that the sacral dermatomes were without sensory involvement. The corneal reflex was preserved. It was again noted that movement of the head and neck resulted in local pain.

Aside from these physical findings, the other available information includes the report of a normal cervical myelogram (February 1953) and the spinal fluid findings three months prior to this admission. The latter report indicates a partial manometric block and an elevated spinal fluid protein. Radiographs of the cervical spine were consistently negative.

The task of localizing this lesion does not seem very formidable. The suboccipital pain, spastic quadriparesis, and sensory involvement as high as the C-2 dermatome without amyotrophy or loss of reflexes of the upper extremities indicate a high cervical cord lesion. The relatively rapid course would be unlikely in syringomyelia and the absence of dissemination, either in space or time, militates against a diagnosis of multiple sclerosis. When confronted with a spinal cord syndrome, adhesive arachnoiditis is always deserving of etiologic consideration. It is not known whether this patient had ever received a spinal anesthetic, but the negative myelography and the rather modest elevation of the cerebrospinal fluid protein do not favor such a diagnosis.

It seems reasonable to conclude that we are dealing with a neoplasm, and we must now attempt to distinguish between an extramedullary and an intramedullary tumor.

The initial symptom, pain in the neck, was characteristically intensified by coughing, sneezing, and cervical flexion. It suggests radicular involvement at about the level of the third cervical cord segment. Although radicular pain is often associated with extramedullary tumors, this is by no means a valuable distinguishing criterion. Webb, Craig, and Kernohan,[1] in a recent review of cervical cord tumors, reported radicular pain in 14 of 24 patients with an intramedullary glioma. The exacerbation of pain with menstruation is difficult to

evaluate. It is occasionally ascribed to a change in pressure relationships associated with premenstrual water retention and the ensuing diuresis.

The sensory dissociation, although traditionally attributed to central lesions of the cord, is another unreliable distinguishing feature. It was found to occur just as frequently with extramedullary neoplasms in the series of 179 cervical cord neoplasms reported by Webb and co-workers. The fact that sensibility was normal over the sacral dermatomes – the so-called "sacral sparing" – suggests that the peripheral laminae of the lateral spinothalamic tracts, which at the cervical level mediate sensation from the sacral dermatomes, were not involved. Presumably, this fact favors a central lesion in the case, but it is probably not sufficient evidence of itself to resolve our diagnostic dilemma.

The absence of a definite sensory level at a time when the neurologic picture is full blown seems another point in favor of an intramedullary site.

While on the subject of the sensory deficit it might be appropriate to allude to the long standing controversy regarding the use of the term "astereognosis." Since we are dealing here with a conduction deficit and not an interruption at the cortical or gnostic level, "stereoanesthesia" might be a more proper designation for the patient's inability to recognize objects by palpation when he is handicapped by a sensory deficit. This problem has recently been reviewed by Boshes and Padberg.[2]

It is pertinent also to consider the nature of the local involvement. The rostral extremity of the cervical cord is implicated, and it is probable that the tumor extends to the level of the foramen magnum, but there is no evidence of involvement of the descending tract of the trigeminal nerve, no nystagmus to imply damage to the vestibulocerebellar connections, and no sign of damage to the lower cranial nerves or nuclei. However, the tremor which was described during the most recent examination may have been related to involvement of spinocerebellar connections in the lower medulla. Nystagmus, dyspnea, dysphagia, hiccup, and dysarthria are not infrequent symptoms in patients with high cervical cord tumors. The selectivity of the pathologic process in this case is perhaps further illustrated by the absence of diaphragmatic weakness, although histologically this disorder might include cervical cord segments 3, 4, and 5. A Horner's syndrome was found by Webb, Craig, and Kernohan in 28 per cent of their cases of intramedullary cervical cord tumor. It is of interest that they found this syndrome just as frequently in high cervical cord tumors as with those in the lower cervical segments. The absence of this feature here is of no diagnostic significance.

The progression of the clinical picture following myelography is of passing interest and points to the necessity for routine reexamination after lumbar puncture of all patients in whom spinal cord tumor is suspected. Lumbar puncture was followed by increase in pain, weakness, or sensory impairment in 19 of the cases in the series mentioned before.[1]

Having indicated how untrustworthy the individual premises may be, it now becomes necessary to rely upon them collectively in order to distinguish between extra- and intramedullary involvement of the spinal cord. Fortified by the relatively remote history of a negative myelogram and only faintly reassured by the fact that the cervical cord is a more common site for the uncommon intramedullary tumor, I conclude that this patient had an intramedullary glioma of the upper cervical cord, which probably involved several segments and was more extensive than the clinical picture would indicate. Since such a glioma is usually an ependymoma or an astrocytoma and

because of the selective infiltration of the process here, one might speculate on the histologic type – although this cannot be more than sheer speculation – and predict an astrocytoma.

CLINICAL DIAGNOSIS

Neoplasm of the upper cervical spinal cord, probably an intramedullary glioma.

DISCUSSION

DR. WILLIAM F. ORR: Although Dr. Sprofkin has dismissed the effect of menstruation and pregnancy on the basis of a nonspecific increase in fluid content of tumors during pregnancy and menstruation, I can't help but wonder if this is not due to vascularity or changes in vascularity. I should like to postulate an intramedullary tumor at the level indicated, possibly a hemangioma or a more vascular tumor than he suggests.

DR. CULLY COBB: I find it difficult to pass lightly over the sensory changes if one assumes that this is an intramedullary tumor. I may be biased because I know of one other patient with findings very similar to these who had extramedullary midline compression from the dorsal side of the cord at the level of C1. I probably would have guessed that this is an extramedullary, dorsally situated neoplasm or a mass of some sort.

An intramedullary lesion at this level, large enough to cause such marked motor changes and the other symptoms that were present here, would in my opinion be expected to cause more definite changes in sensation in the lower and upper extremities. These seem to be rather spotty and indefinite and there is not a sensory level. In order to get as many changes in proprioception and motor power as one has here, an intramedullary lesion would have to be quite large.

DR. WILLIAM MEACHAM: This patient was operated upon on November 25, 1953. Under general endotracheal ether anesthesia, in the face-down cerebellar position, a high cervical laminectomy (C1-C3) was carried out. The dura was opened in linear fashion at the C3 level; as the dura was opened, the inferior surface of an intradural mass was noted. This mass was seen to occupy the right posterolateral portion of the upper cervical canal. The superior portion of the tumor disappeared beneath the foramen magnum. The suboccipital bone about the foramen magnum was removed. The dural incision was extended up into the dura covering the cerebellar hemispheres.

The dorsal surface of the tumor was fully exposed by this additional maneuver. It was a rather nodular but smoothly encapsulated mass, not invading the cord or inferior medulla. The tumor extended from its attachment at the foramen magnum caudad to the level of the third cervical segment, occupying the right side of the spinal canal (figure 2). The upper cervical cord and inferior medulla were gently freed from the adhesions which attached the capsule of the tumor to the cord and medulla, and by gently rocking the tumor from its nidus, it could be seen that the point of attachment was at the inferior rim of the lateral foramen magnum. As soon as the tumor was mobilized sufficiently to allow its being turned laterally on its pedicle, this was done. The attachment was severed by sharp deflection and the tumor removed. This procedure was well tolerated.

DR. DODGE: On gross examination the tumor was very firm and cut with moderate resistance. The cut surface was smooth and pearly gray in color. Numerous bands of connective tissue traversed the tumor, producing multiple lobulations. The histologic pattern was typical of a psammomatous meningioma (figure 3). There were compact islands of plump, oval, vesicular nuclei. The cells contained a small amount of cytoplasm. Many of these cells formed tight whorls, some of which were hyalinized

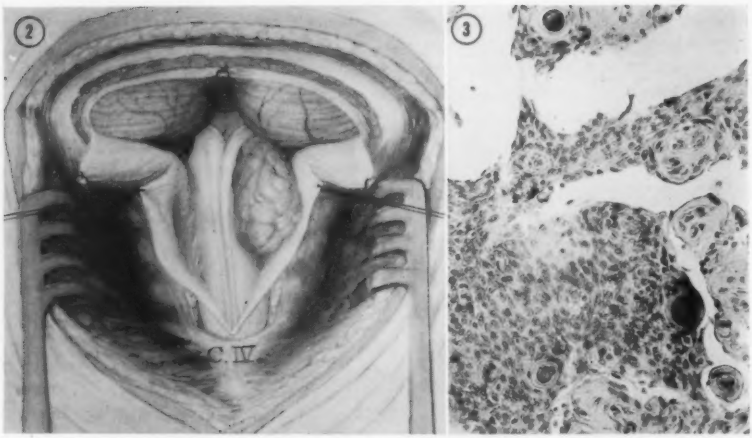


FIG. 2. Operative sketch. Note the compression and distortion of the cervical cord.
FIG. 3. Histologic appearance of the tumor demonstrating its cellularity, whorls, and psammoma bodies. Hematoxylin and eosin.

and a few calcified.

Recovery of function in this patient has been most gratifying to everyone. Within the first day or two after operation there was increased strength and sensation in the hands and arms. At the time of discharge from the hospital about two weeks later, it was difficult to demonstrate any abnormal neurologic signs. There was minimal weakness of the posterior neck muscles on the right side and the patient still tired easily. In the ensuing weeks she resumed all the activities that her illness had forced her to forego. Currently she is successfully managing a household of four children.

Dr. Sprofkin has emphasized the usual futility of attempting to distinguish on clinical grounds alone between an intramedullary, usually nonremediable, and an extramedullary, often remediable, tumor. The importance of this fact is obvious. The dilemma can be resolved only by exploration, and such a course of action should certainly be undertaken in all such cases. Many of us who saw this patient prior to operation feared that the pathologic process was intramedullary. On the other hand, Dr. Charles W. Cure and Dr. Paul Garvey were more optimistic and strongly suspected the correct diagnosis. I believe that their conclusion was influenced mostly by the location and character of the pain. In a recent article on foramen magnum meningioma, Piehl, Reese, and Steelman[3] emphasized the fact that suboccipital pain and disturbance of neck motion, antedating other symptoms and signs by many months or years, are quite typical features. The incidence of such tumors is indicated by the fact that during a ten year period these authors encountered three cases of foramen magnum meningioma and 57 cases of meningioma at various other sites along the neuraxis.

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# NEWSLETTER

OCTOBER, 1954

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AMERICAN ACADEMY OF NEUROLOGY

**Public Health Service Research Grant Awards** As of August 5, 1954, the Public Health Service, U. S. Department of Health, Education, and Welfare, approved 1,442 research projects, totaling $14,685,671, for basic and applied medical research in universities and research centers. Four hundred and fifty-nine of these awards, totaling $4,568,073, were for new research projects; while 983, totaling $10,117,598, were for continuation of existing projects. The awards were made to scientists in 335 research institutions in the United States and are administered by the National Institutes of Health, the research arm of the Public Health Service.... Of this total, 55 new grant awards ($471,178) and 140 continuations ($1,327,089) were approved for the National Institute of Neurological Diseases and Blindness. The next deadline for NINDB research grant applications is November 1, 1954. Research grant applications are reviewed by special Study Sections (panels of technical experts) and then referred to the NINDB National Advisory Council (a group of prominent scientists and nonprofessional individuals), which makes final recommendations to the Surgeon General of the Public Health Service.... New 1954 appointments to this Council are: H. Houston Merritt (second term to fill the expired term of Henry W. Woltman); Louis Sanford Goodman, Professor of Pharmacology, University of Utah Medical School; Mrs. Helen Hamilton Woods, formerly Deputy Director of the Women's Army Corps; and Mr. Roy Laos, head and owner of Old Pueblo Bus Company, Tucson, Arizona.

**Neurological Surgeons To Meet In New York** The Congress of Neurological Surgeons will meet at the Waldorf Astoria Hotel in New York, November 4 - 6, 1954. Featured as honored guest is Dr. Kenneth McKenzie of Toronto, who will give papers on special aspects of Brain Tumors, Sympathectomy, Spasmodic Torticolis, Meniere's Syndrome, and the Results Following Tractotomy for Trigeminal Neuralgia. In addition there will be symposia led by Frank Mayfield of Cincinnati and Howard A. Rusk of New York, which are to be followed by panel discussions in which leading authorities will participate. Another panel discussion on the Medico Legal Aspects of Head Injuries will have A. Earl Walker as moderator, and will include in the

program, William F. Caveness, Dean Roscoe L. Barrow of the University of Cincinnati College of Law, and Mr. W. Scott Alan of the Liberty Mutual Insurance Company.... Inquiries concerning the meeting should be addressed to Dr. Henry M. Suckle, 414 Tenney Building, Madison 3, Wisconsin.

**Connecticut Seminar In Neurology and Psychiatry** The 8th Connecticut postgraduate seminar in neurology and psychiatry began September 27, 1954, and will continue through May 9, 1955. Sessions in clinical neurology, neuroroentgenology, electroencephalography, neuroanatomy, neurophysiology, and neuropathology will be held on Mondays and Wednesdays at the Yale University School of Medicine from January 3 through February 28, 1955. The sessions in general psychiatry will be held at the Connecticut State Hospital in Middletown from January 3 to February 28, 1955, while from March 7 through April, courses will be given in child psychology on Mondays; and through April 11 to May 9, also on Mondays, there will be a course in pediatric neurology at Yale University School of Medicine.... No fees are required for these courses. Copies of the program may be obtained from the Assistant Dean of Postgraduate Education, Yale University, 333 Cedar Street, New Haven, Connecticut.

**American PMR Congress Meets In Washington** The American Congress of Physical Medicine and Rehabilitation held its 32nd annual scientific and clinical session at the Hotel Statler in Washington from September 6 to 11. Included in the program were papers on the conduction velocity of motor nerves in neuromuscular disorders (Henriksen and Lambert); EMG studies of respiratory muscles and symposia on poliomyelitis, ultrasonic therapy, and cerebral palsy.... In conjunction with the Congress, there was an instruction seminar on the management of hemiplegia, low back pain and osteoarthritis.... Preceding the Congress and also at the Statler, the American Institute of Ultrasonics in Medicine held its third annual conference.

* * * * * *

**Brown Comments On Danish Neurology** Continuing the neurologic peripatetics of Joe R. Brown last summer (see February, April, and September, 1954, Newsletters), he also gives a provocative account of his trip to Copenhagen where he made rounds with the illustrious Professor Knud H. Krabbe, Neurological Clinic of the University of Copenhagen, observing him in the examination of a patient with encephalitis and having the opportunity to review some of Professor Krabbe's famous specimens in neuroembryology. Also, through the courtesy of

Dr. Erna Christensen, now working on polymyositis and other neuromuscular disorders, he visited the neurologic unit of the National Hospital which has about 120 neurologic beds and 65 neurosurgical beds, with new construction under way for the expansion of these facilities. Considerable interest was expressed in the management of multiple sclerosis, a common neurologic problem in Scandinavian countries. At the Copenhagen Community Hospital, Dr. Vraa-Jensen showed his neuropathology laboratory and demonstrated a case of calcification in the cerebellum and of the cerebellar cortex. Also in Copenhagen, he visited the Community Hospital at Fredricksburg, under the direction of Dr. Dahlsgaard-Nielsen who is pursuing studies on headache and rehabilitation of the disabled and the aged.... According to Brown, neurological training in Denmark comprises two years in general medicine and surgery, three years residency in neurology, and one-half year each of psychiatry and neurosurgery. Basic science training is given simultaneously with neurologic training.

**Baker To Visit Norway** At invitations from Professors Monrad-Krohn and Sigvald Refsum, A. B. Baker will visit the University of Oslo this month, to deliver five lectures to medical school classes on the diagnostic and therapeutic aspects of modern clinical neurology. In addition he will give a public address on poliomyelitis, and a lecture on the hypothalamus to the Norwegian Neurological Society. From Oslo he will proceed to Bergen, where he again will present a series of lectures to medical school classes. His trip terminates in a visit to Stockholm and Copenhagen, after which he returns to the U. S. on November 15.

**Russell Brain Speaks On British Medicine** Recently in Chicago, Sir E. Russell Brain, noted English neurologist and president of the Royal College of Physicians, and Lady Brain presented a discussion on "Some Aspects of British Medicine" before the American College of Physicians. A tape recording of the talk was made and is available upon request from the British Information Service, 720 North Michigan Avenue, Chicago 11, Illinois.

* * * * * *

**Here And There** The American Association of Electromyography and Electrodiagnosis held its annual scientific session in the Statler Hotel, Washington, D. C. September 5, 1954. The sessions centered on terminology and definitions in electrodiagnosis; studies on the myotonias, myasthenia gravis, myositis, and root compression syndromes. James G. Golseth is president of the Society, Arthur A. Rodriquez, secretary-treasurer, and

Jerome W. Gersten, chairman of the Program Committee.... The Michigan Society of Neurology and Psychiatry offers an annual award of $250 for the outstanding piece of research in neurology, psychiatry, their basic sciences, or allied fields of interest. The research must be achieved within the first five years of specialty training or experience. The award is open to researchers living in Michigan, north central Ohio, and the province of Ontario, Canada, and in the area contiguous to the State of Michigan. Inquiries should be addressed to Dr. Ivan C. Berlien, chairman, 1753 Guardian Building, Detroit 26.... Christian Herrmann, formerly associated with Houston Merritt at the New York Neurological Institute, has joined the teaching staff of Augustus S. Rose at U.C.L.A. His special interest is in neuromuscular disease, particularly myasthenia gravis.... The 1954 Thirty-first Convention of the National Society for Crippled Children and Adults will be held at the Hotel Statler, Boston, November 2, through noon, November 6.... The National Committee for Research in Neurological Disorders (see July, 1954, Newsletter) held its fall meeting in Washington, D. C., September 8, with A. B. Baker presiding.... Dr. Werner Scheid, professor of neurology and psychiatry and director of the Universitats-Nervenklinik, Cologne, Germany, will visit the U. S. as a Fulbright scholar, beginning September 18.... Francis M. Forster, program chairman of the 1955 annual AAN meeting in Houston, Texas, reports that abstracts for papers for the scientific sessions are being submitted. The deadline for such abstracts is January 15, 1955....

Pearce Bailey

# Neurology BOOK REVIEWS

## Neurosurgery of Infancy and Childhood

*Franc D. Ingraham, M.D. and Donald D. Matson, M.D. 1954. Springfield, Illinois: Charles C Thomas, Publisher. 456 pages, 381 illustrations, $15.00.*

IN THIS handsome monograph the authors discuss in detail the problems encountered in pediatric neurosurgery. It is well known that the neurologic conditions encountered in infancy and childhood differ in many respects from those of adult life. It is, therefore, proper that the first third of this book is devoted to the consideration of congenital anomalies. Because of their special interest in this subject and their previous contributions to it, the authors have given an exceptionally fine account of the treatment of the malformations of the nervous system.

The second third of the book deals with brain tumors in an orthodox manner and few neurosurgeons would disagree with their conclusions. Because the average neurosurgeon is rarely called upon to treat brain tumors in children, this discussion by surgeons with an extensive experience working in a children's hospital should be particularly welcome.

The last third of the book covers such subjects as infection, cerebrovascular disorders, epilepsy, and lead encephalopathy, but is not as interesting or well presented as the first parts of the monograph. An adequate bibliography and index are appended. Special mention should be made of the excellent illustrations which adorn almost every page of the book.

This is an excellent and authoritative presentation of the subject and should be read by every neurologist, neurosurgeon, and pediatrician. Students will find it useful as a reference volume.

A. E. W.

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## The Painful Phantom: Psychology, Physiology, Treatment

*Lawrence C. Kolb, M.D. American Lecture Series No. 235. 1954. Springfield, Illinois: Charles C Thomas, Publisher. 50 pages, $1.50.*

THOSE INTERESTED in the problem of the painful phantom limb following amputation will find in this short and authoritative monograph an outline of the clinical features of the phenomenon, a clear exposition of the major neurologic and psychologic theories in the frame work of which the interpretation of the phenomenon is proposed, and an outline of the program of the psychotherapeutic management of the patients who have undergone or are about to undergo the loss of a part of the body by amputation.

The author presents his argument in the light of a personal psychiatric experience with the amputees at Mayo Clinic.

He sets his theoretical envisagement of the psycho-physiologic mechanism of painful phantom squarely in the frame work of Freudian postulates and premises, tempered by the consideration of the practical necessities of clinical medicine.

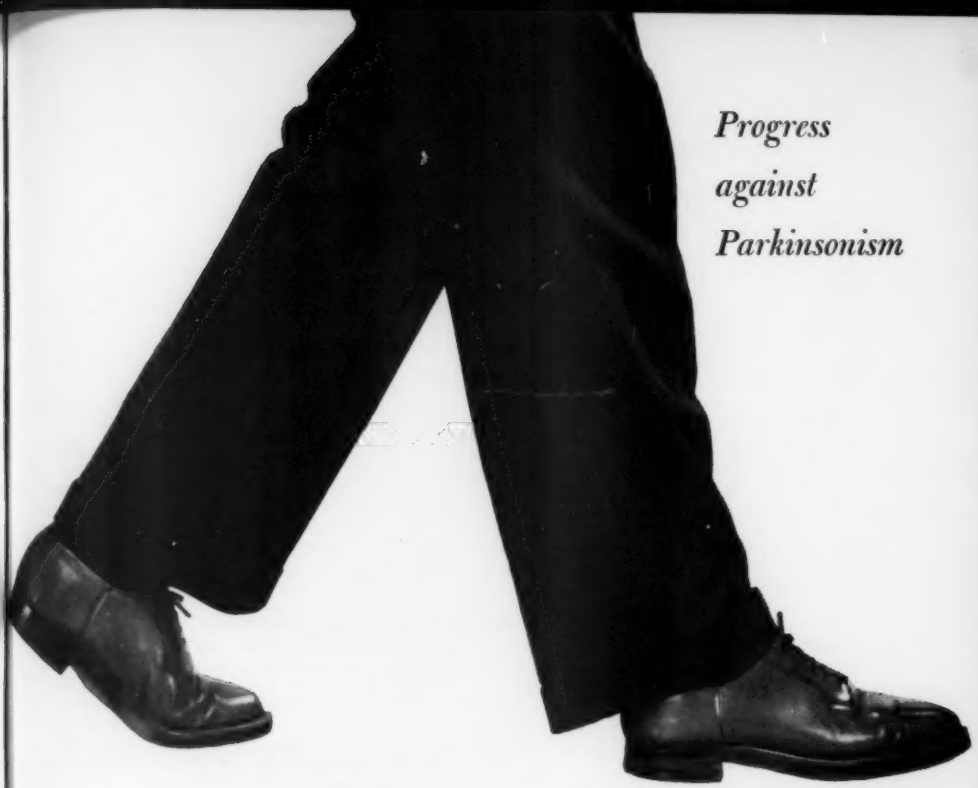
In the main, the author's argument unfolds as follows: The complaint of pain is more than percept of pain; the phenomena of lasting after-discharge through reverberating circuits in the internuncial neuronal pools, sustained by the *centripetal stimuli* from stump and other algogenic zones of the periphery, as proposed by William K. Livingston, provide the frame work for a plausible interpretation of the physiologic causality of the pain percept; however, the states of fear, perceptions, and associated ideas may be assumed to occur concomitantly with the electric and metabolic processes in the brain and may in turn influence the excitability of the internuncial pools at both the suprasegmental and spinal levels through *centrifugal impulses,* thus producing the percept of pain in the phantom part by a "feedback" mechanism.

This point of the argument opens the door for at least a pragmatic marriage of the mechanics of the pain percept with the dynamics of personal motivation of the pain complaint. The personal frustrations of the loss of a part may, under certain conditions, become charged with a symbolic meaning of other ancient or present but subjugated frustrations in the patient's life experience; and so, in the words of one of the author's patients, the pain of the phantom may become literally a "sympathetic pain" referred as it were to the missing part from other psychic algogenic zones of his intimate self. From this theoretical premise the author's argument runs on empirical evidence of his clinical observations couched in stark Freudian formulae. In the outset of the monograph he refers to Freud's interpretation of the psychogeny of "hysterical algias" and in the body of the book cites examples from his own experience at Mayo Clinic which show that in some patients the pain in the phantom part is evocable or is emphatically enhanced whenever some upsetting matters in the patient's relationships with other significant persons in his life history are touched on or encroached upon. Three case histories are cited in detail.

A curiously intriguing observation of the author is that of 21 amputees with painful phantom, 14 have indicated some significant affect-charged association with an amputee in the past; such an amputee-figure was uncommon in the histories of normal individuals and in the control groups of nonamputees. The author concludes that the failure of an amputee to make satisfactory adjustment to the loss of a part and the persistence of painful phantom suggests the existence of personality disturbances. Such liabilities in the intimate spheres of the patient's life experience should be detected early when appropriate psychotherapy may still be instituted with a reasonable hope to help the patients with a relative ease.

The author illustrates this point with the examples of satisfactory results of short psychotherapy in such early recognized psychologic complications of the amputations. A quotation from Guy de Chauliac, a XIV-century surgeon, illuminates delightfully the author's discussion of the argument. Once, however, the deterministic physiologic causality of the pain percept has become agglutinated in the patient's mind with the finalistic causality of the psychologic motivations of the pain complaint, the causes of complaint are then not readily absolved from the causes of percept of pain; the causal complex of painful phantom becomes fixed and its resolution by psychotherapy is immeasurably more difficult.

P. I. Y.



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**References:** 1. Gallagher, D. J. A., and Palmer, H.: New Zealand M. J. *49*:531 (Oct.) 1950. 2. Sigwald, J.: Presse méd. *59*:819 (Sept. 17) 1949. 3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. *247*:98 (July 17) 1952.

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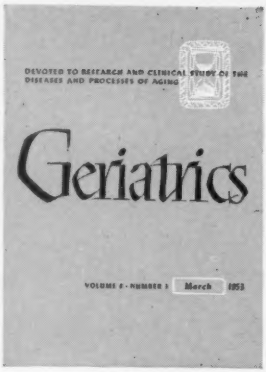


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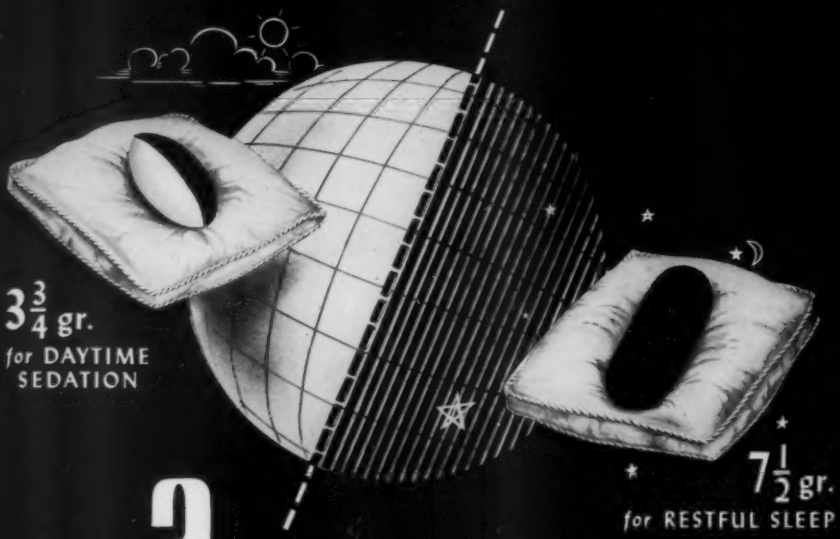


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